CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125057Orig1s232

Trade Name:	**HUMIRA**
Generic or Proper Name:	**adalimumab**
Sponsor:	**Abbvie Inc.**
Approval Date:	**09/28/2012**
Indication:	HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:

Rheumatoid Arthritis (RA)

• Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA)

• Reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 4 years of age and older.

Psoriatic Arthritis (PsA)

• Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS)

• Reducing signs and symptoms in adult patients with active AS.

Crohn’s Disease (CD)

• Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC)

• Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (Ps)

• The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA125057Orig1s232

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/232

SUPPLEMENT APPROVAL

Abbott Laboratories
Attention: Bonnie Kain
Associate Director, Regulatory Affairs – PPG
200 Abbott Park Road
Abbott Park, IL 60064

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA), dated January 25, 2011, and received March 30, 2012, submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We acknowledge receipt of your amendments dated March 25, 2011, April 28, 2011, May 24, 2011, May 27, 2011, June 06, 2011, July 25, 2011, July 27, 2011, September 21, 2011, September 29, 2011, October 07, 2011, October 12, 2011, March 30, 2012, July 23, 2012, July 27, 2012, August 01, 2012, August 15, 2012, August 22, 2012, September 17, 2012, September 18, 2012, and September 26, 2012.

The March 30, 2012, submission constituted a complete response to our November 21, 2011, action letter.

This Prior Approval supplemental biologics application proposes the addition of a new indication for Humira (adalimumab) for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert,

Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125057/232.**"

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your March 25, 2011, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because an orphan designation was granted for your pediatric indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Humira (adalimumab) was approved on December 31, 2002, we have become aware of additional cases of Hepatosplenic T-cell Lymphoma (HSTCL), a rare form of malignancy, in patients with inflammatory bowel disease (IBD) receiving Humira (adalimumab). In addition, there are literature reports of an increased risk of serious adverse events in patients receiving

higher doses of Humira (adalimumab), including opportunistic infections and malignancies.[1] We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of HSTCL and other serious adverse events in patients receiving higher doses of adalimumab, including opportunistic infections and malignancies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #1 A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

The timetable you submitted on September 26, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	09/2019
Final Report Submission:	09/2020

PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-

[1] Bongartz T, et.al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17;295(19):2275-85.

treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Study Completion:	12/2027
Final Report Submission:	12/2029

PMR #3 Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission:	12/2013

PMR #4 Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	03/2018
Final Report Submission:	03/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known risk of serious adverse events, including opportunistic infections and malignancies, in patients receiving higher doses of adalimumab.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #5 Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

PMR #6 A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

Submit the protocols to your IND 100103 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC #7 Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	06/2013
Trial Completion:	06/2018
Final Report Submission:	12/2019

Submit clinical protocols to your IND 100103 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Division Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW E MULBERG

09/28/2012

Division Deputy Director
DGIEP
Signatory Authority

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/232

COMPLETE RESPONSE
November 21, 2011

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

We acknowledge receipt of your amendments dated March 25, 2011, April 28, 2011, May 24, 2011, May 27, 2011, June 06, 2011, July 25, 2011, July 27, 2011, September 21, 2011, September 29, 2011, October 07, 2011, and October 12, 2011.

This "Prior Approval" efficacy supplement to your biologics license application proposes to add the indication of reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are two-fold.

   First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated

patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

Second, we are concerned that you may not have adequately selected an appropriate adalimumab dose for your pivotal efficacy trials. We note the modest improvement in clinical remission rates reported in both trials (treatment differences relative to placebo in clinical remission at Week 8 of 9.3% and 7.2% in Studies M06-826 and M06-827, respectively), and the treatment difference relative to placebo in sustained clinical remission (at both Weeks 8 and 52) of 4.4% in Study M06-827.

To address these concerns, we will need to seek expert advice at a future meeting of the Gastrointestinal Drugs Advisory Committee.

LABELING

2. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

3. During a recent inspection of the (b) (4) facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Although these are not approvability issues at this time, we request that you respond to the following comments in your re-submission:

IMMUNOGENICITY

1. The immunogenicity assay was not adequate because the original and new immunogenicity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. Therefore, there is a need to develop an assay with improved drug tolerance.

   To address this issue, you should develop, qualify and implement an improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed

description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patient samples collected from clinical studies should be banked under appropriate storage conditions.

2. The immunogenicity profile for adalimumab has not been adequately assessed.

   Utilizing a validated AAA assay as described in Item #1 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay.

STATISTICAL

3. STUDY M06-826

   a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP < 10.0 mg/L vs. CRP ≥10.0 mg/L (13.4% vs. -4.5%).

4. STUDY M06-827

   a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

   b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% vs. 12.1%.

   c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary

endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on "Formal Meetings Between FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

Andrew E Mulberg MD, FAAP

/ ANDREW E. MULBERG/
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Division Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMIRA safely and effectively. See full prescribing information for HUMIRA.

HUMIRA (adalimumab) injection, for subcutaneous use

Initial U.S. Approval: 2002

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS (5.1, 6.1):

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.**
- **Discontinue HUMIRA if a patient develops a serious infection or sepsis during treatment.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting HUMIRA.**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative.**

MALIGNANCY (5.2):

- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA.**
- **Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.**

-------RECENT MAJOR CHANGES-------

Indications and Usage, Ulcerative Colitis (1.6) ---------- 9/2012
Dosage and Administration, Ulcerative Colitis (2.4) ------- 9/2012
Warnings and Precautions, Neurologic Reactions (5.5) --- 12/2011

-------INDICATIONS AND USAGE-------

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1):

- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Juvenile Idiopathic Arthritis (JIA) (1.2):

- Reducing signs and symptoms of moderately to severely active polyarticular JIA in pediatric patients 4 years of age and older.

Psoriatic Arthritis (PsA) (1.3):

- Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.

Ankylosing Spondylitis (AS) (1.4):

- Reducing signs and symptoms in adult patients with active AS.

Crohn's Disease (CD) (1.5):

- Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Ulcerative Colitis (UC) (1.6):

- Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis (Ps) (1.7):

- The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

-------DOSAGE AND ADMINISTRATION-------

- Administered by subcutaneous injection (2)

Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis (2.1):

- 40 mg every other week.
  - Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

Juvenile Idiopathic Arthritis (2.2):

- *15 kg (33 lbs) to < 30 kg (66 lbs)* 20 mg every other week
- *≥ 30 kg (66 lbs)* 40 mg every other week

Crohn's Disease and Ulcerative Colitis (2.3, 2.4):

- Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days)
- Second dose two weeks later (Day 15): 80 mg
  - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
- For patients with Ulcerative Colitis only: Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Plaque Psoriasis (2.5):

- 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.

-------DOSAGE FORMS AND STRENGTHS-------

- Injection: 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) (3)
- Injection: 40 mg/0.8 mL in a single-use prefilled glass syringe (3)
- Injection: 20 mg/0.4 mL in a single-use prefilled glass syringe (3)

-------CONTRAINDICATIONS-------

None (4)

-------WARNINGS AND PRECAUTIONS -------

- *Serious infections* Do not start HUMIRA during an active infection. If an infection develops, monitor carefully, and stop HUMIRA if infection becomes serious (5.1)
- *Invasive fungal infections* For patients who develop a systemic illness on HUMIRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1)
- *Malignancies* Incidence of malignancies was greater in HUMIRA-treated patients than in controls (5.2)
- *Anaphylaxis or serious allergic reactions* may occur (5.3)
- *Hepatitis B virus reactivation* Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop HUMIRA and begin anti-viral therapy (5.4)
- *Demyelinating disease* Exacerbation or new onset, may occur (5.5)
- *Cytopenias, pancytopenia* Advise patients to seek immediate medical attention if symptoms develop, and consider stopping HUMIRA (5.6)
- *Heart failure* Worsening or new onset, may occur (5.8)
- *Lupus-like syndrome* Stop HUMIRA if syndrome develops (5.9)

-------ADVERSE REACTIONS-------

Most common adverse reactions (incidence >10%): infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-------DRUG INTERACTIONS-------

- *Abatacept* Increased risk of serious infection (5.1, 5.11, 7.2)
- *Anakinra* Increased risk of serious infection (5.1, 5.7, 7.2)
- *Live vaccines* Avoid use with HUMIRA (5.10, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:
• Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.
• Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
• Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions (5.2)]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see*

Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

1.2 Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

1.3 Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

1.4 Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

1.5 Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

1.6 Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers *[see Clinical Studies (14.6)]*.

1.7 Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less

appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

HUMIRA is administered by subcutaneous injection.

2.1 Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg administered every other week. Methotrexate (MTX), other non-biologic DMARDS, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with HUMIRA. In the treatment of RA, some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

2.2 Juvenile Idiopathic Arthritis

The recommended dose of HUMIRA for pediatric patients 4 to 17 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HUMIRA.

Pediatric Patients (4 to 17 years)	**Dose**
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week (20 mg Prefilled Syringe)
≥30 kg (66 lbs)	40 mg every other week (HUMIRA Pen or 40 mg Prefilled Syringe)

Limited data are available for HUMIRA treatment in pediatric patients with a weight below 15 kg.

2.3 Crohn's Disease

The recommended HUMIRA dose regimen for adult patients with Crohn's disease (CD) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine, 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* or MTX may be continued during treatment with HUMIRA if necessary. The use of HUMIRA in CD beyond one year has not been evaluated in controlled clinical studies.

2.4 Ulcerative Colitis

The recommended HUMIRA dose regimen for adult patients with ulcerative colitis (UC) is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) continue with a dose of 40 mg every other week.

Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Aminosalicylates and/or corticosteroids may be continued during treatment with HUMIRA. Azathioprine and 6-mercaptopurine (6-MP) *[see Warnings and Precautions (5.2)]* may be continued during treatment with HUMIRA if necessary.

2.5 Plaque Psoriasis

The recommended dose of HUMIRA for adult patients with plaque psoriasis (Ps) is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of HUMIRA in moderate to severe chronic Ps beyond one year has not been evaluated in controlled clinical studies.

2.6 Monitoring to Assess Safety

Prior to initiating HUMIRA and periodically during therapy, evaluate patients for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

2.7 General Considerations for Administration

HUMIRA is intended for use under the guidance and supervision of a physician. A patient may self-inject HUMIRA if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

Carefully inspect the solution in the HUMIRA Pen or prefilled syringe for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, do not use the product. HUMIRA does not contain preservatives; therefore, discard unused portions of drug remaining from the syringe. NOTE: Instruct patients sensitive to latex not to handle the needle cover of the syringe because it contains dry rubber (latex).

Instruct patients using the HUMIRA Pen or prefilled syringe to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

Instruct patients (15 kg to <30 kg) using the pediatric pre-filled syringe, or their caregivers, to inject the full amount in the syringe (0.4 mL), which provides 20 mg of HUMIRA, according to the directions provided in the Instructions for Use.

Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

3 DOSAGE FORMS AND STRENGTHS

- **Pen**

Injection: A single-use pen (HUMIRA Pen), containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

- **Prefilled Syringe**

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA.

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 20 mg (0.4 mL) of HUMIRA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions (5.7, 5.11) and Drug Interactions (7.2)]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating HUMIRA, assess if treatment for latent tuberculosis is needed; and consider an induration of ≥ 5 mm a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

5.2 Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult

patients. During the controlled portions of 34 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) and plaque psoriasis (Ps), malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.6 (0.38, 0.91) per 100 patient-years among 7304 HUMIRA-treated patients versus a rate of 0.6 (0.30, 1.03) per 100 patient-years among 4232 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, and Ps, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1]

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, and Ps, the rate (95% confidence interval) of NMSC was 0.7 (0.49, 1.08) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.08, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, 3 lymphomas occurred among 7304 HUMIRA-treated patients versus 1 among 4232 control-treated patients. In 47 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of approximately 0.6 years, including 23,036 patients and over 34,000 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).[1] Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use

in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

5.3 Hypersensitivity Reactions

In postmarketing experience, anaphylaxis and angioneurotic edema have been reported rarely following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

5.4 Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. For patients who are carriers of HBV and require treatment with TNF blockers, closely monitor such patients for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy

with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of HUMIRA therapy in this situation and monitor patients closely.

5.5 Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders.

5.6 Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

5.7 Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions (7.2)]*.

5.8 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

5.9 Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions (6.1)]*.

5.10 Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Similar proportions of patients developed protective levels of anti-influenza antibodies between HUMIRA and placebo treatment groups; however, titers in aggregate to influenza antigens were moderately lower in patients receiving HUMIRA. The clinical significance of this is unknown. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

5.11 Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions (7.2)]*.

6 ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions

leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 34 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC and Ps, the rate of serious infections was 4.6 per 100 patient-years in 7304 HUMIRA-treated patients versus a rate of 3.1 per 100 patient-years in 4232 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions (5.1)]*.

Tuberculosis and Opportunistic Infections

In 47 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC and Ps that included 23,036 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.22 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. In a subgroup of 9396 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.07 per 100 patient-years and the rate of positive PPD conversion was 0.08 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.08 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions (5.1)]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in patients with CD with control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively,

followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with JIA, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In patients with CD, the rate of antibody development was 3%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. The

observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
	(N=705)	(N=690)
Adverse Reaction (Preferred Term)		
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%

Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%
* Laboratory test abnormalities were reported as adverse reactions in European trials ** Does not include injection site erythema, itching, hemorrhage, pain or swelling		

Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies

Other infrequent serious adverse reactions that do not appear in the Warnings and Precautions or Adverse Reaction sections that occurred at an incidence of less than 5% in HUMIRA-treated patients in RA studies were:

Body As A Whole: Pain in extremity, pelvic pain, surgery, thorax pain

Cardiovascular System: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia

Digestive System: Cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, hepatic necrosis, vomiting

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, polycythemia

Metabolic And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema

Musculo-Skeletal System: Arthritis, bone disorder, bone fracture (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder

Neoplasia: Adenoma

Nervous System: Confusion, paresthesia, subdural hematoma, tremor

Respiratory System: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated pediatric patients in the juvenile idiopathic arthritis (JIA) trial were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions*

(5), Adverse Reactions (6)]. Important findings and differences from adults are discussed in the following paragraphs.

HUMIRA was studied in 171 pediatric patients, 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

A total of 45% of children experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in children receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment, non-serious hypersensitivity reactions were seen in approximately 6% of children and included primarily localized allergic hypersensitivity reactions and allergic rash.

Isolated mild to moderate elevations of liver aminotransferases (ALT more common than AST) were observed in children with JIA exposed to HUMIRA alone; liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment.

In the JIA trial, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of children treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK). Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 patients with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for patients with Ps treated with HUMIRA was similar to the safety profile seen in patients with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps patients, HUMIRA-treated patients had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

Hepato-biliary disorders: Liver failure

Immune system disorders: Sarcoidosis

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX *[see Clinical Pharmacology (12.3)]*.

7.2 Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions (5.7 and 5.11)]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information to provide recommendations regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps.

7.3 Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions (5.10)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneously with methotrexate every week or 373 times human AUC when given 40 mg subcutaneously without methotrexate) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HUMIRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) have not been established.

Juvenile Idiopathic Arthritis

In the JIA trial, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies (14.2)]*. HUMIRA has not been studied in children less than 4 years of age, and there are limited data on HUMIRA treatment in children with weight <15 kg.

The safety of HUMIRA in pediatric patients in the JIA trial was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions (6.1)]*.

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

10 OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a

process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-use, 1 mL prefilled glass syringe. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2.

Each prefilled syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

Each pediatric prefilled syringe delivers 0.4 mL (20 mg) of drug product. Each 0.4 mL of HUMIRA contains 20 mg adalimumab, 2.47 mg sodium chloride, 0.34 mg monobasic sodium phosphate dihydrate, 0.61 mg dibasic sodium phosphate dihydrate, 0.12 mg sodium citrate, 0.52 mg citric acid monohydrate, 4.8 mg mannitol, 0.4 mg polysorbate 80, and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In Ps, treatment with HUMIRA may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which HUMIRA exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

12.2 Pharmacodynamics

After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease and ulcerative colitis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

12.3 Pharmacokinetics

The maximum serum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were 4.7 ± 1.6 μg/mL and 131 ± 56 hours respectively, following a single 40 mg subcutaneous administration of HUMIRA to healthy adult subjects. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. The pharmacokinetics of adalimumab were linear over the dose range of 0.5 to 10.0 mg/kg following a single intravenous dose.

The single dose pharmacokinetics of adalimumab in RA patients were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L. The systemic clearance of adalimumab is approximately 12 mL/hr. The mean terminal half-life was approximately 2 weeks, ranging from 10 to 20 days across studies. Adalimumab concentrations in the synovial fluid from five rheumatoid arthritis patients ranged from 31 to 96% of those in serum.

In RA patients receiving 40 mg HUMIRA every other week, adalimumab mean steady-state trough concentrations of approximately 5 μg/mL and 8 to 9 μg/mL, were observed without and with methotrexate (MTX), respectively. MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively, in patients with RA. Mean serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40, and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

Adalimumab mean steady-state trough concentrations were slightly higher in psoriatic arthritis patients treated with 40 mg HUMIRA every other week (6 to 10 μg/mL and 8.5 to 12 μg/mL, without and with MTX, respectively) compared to the concentrations in RA patients treated with the same dose.

The pharmacokinetics of adalimumab in patients with AS were similar to those in patients with RA.

In patients with CD, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 μg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 μg/mL were observed at Week 24 and Week 56 in CD patients after receiving a maintenance dose of 40 mg HUMIRA every other week.

In patients with UC, the loading dose of 160 mg HUMIRA on Week 0 followed by 80 mg HUMIRA on Week 2 achieves mean serum adalimumab trough levels of approximately 12 μg/mL at Week 2 and Week 4. Mean steady-state trough level of approximately 8 μg/mL was observed at Week 52 in UC patients after receiving a dose of 40 mg HUMIRA every other week, and approximately 15 μg/mL at Week 52 in UC patients who increased to a dose of 40 mg HUMIRA every week.

In patients with Ps, the mean steady-state trough concentration was approximately 5 to 6 μg/mL during HUMIRA 40 mg every other week monotherapy treatment.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of adalimumab in the presence of anti-adalimumab antibodies, and lower clearance with increasing age in patients aged 40 to >75 years.

Minor increases in apparent clearance were also predicted in RA patients receiving doses lower than the recommended dose and in RA patients with high rheumatoid factor or CRP concentrations. These increases are not likely to be clinically important.

No gender-related pharmacokinetic differences were observed after correction for a patient's body weight. Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

In subjects with JIA (4 to 17 years of age), the mean steady-state trough serum adalimumab concentrations for subjects weighing <30 kg receiving 20 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.8 μg/mL and 10.9 μg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for subjects weighing ≥30 kg receiving 40 mg HUMIRA subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.6 μg/mL and 8.1 μg/mL, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥18 years of age with active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 swollen and 9 tender joints. HUMIRA was administered subcutaneously in combination with methotrexate (MTX) (12.5 to 25 mg, Studies RA-I, RA-III and RA-V) or as monotherapy (Studies RA-II and RA-V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study RA-IV).

Study RA-I evaluated 271 patients who had failed therapy with at least one but no more than four DMARDs and had inadequate response to MTX. Doses of 20, 40 or 80 mg of HUMIRA or placebo were given every other week for 24 weeks.

Study RA-II evaluated 544 patients who had failed therapy with at least one DMARD. Doses of placebo, 20 or 40 mg of HUMIRA were given as monotherapy every other week or weekly for 26 weeks.

Study RA-III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study RA-III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 5 years.

Study RA-IV assessed safety in 636 patients who were either DMARD-naive or were permitted to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of HUMIRA or placebo every other week for 24 weeks.

Study RA-V evaluated 799 patients with moderately to severely active RA of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40 mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies RA-II and III are shown in Table 2.

Table 2. ACR Responses in Studies RA-II and RA-III (Percent of Patients)

	Study RA-II Monotherapy (26 weeks)			**Study RA-III Methotrexate Combination (24 and 52 weeks)**	
Response	Placebo	HUMIRA	HUMIRA	Placebo/MTX	HUMIRA/MTX
		40 mg every	40 mg weekly		40 mg every
		other week			other week
	N=110	N=113	N=103	N=200	N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*
* $p<0.01$, HUMIRA *vs.* placebo					

The results of Study RA-I were similar to Study RA-III; patients receiving HUMIRA 40 mg every other week in Study RA-I also achieved ACR 20, 50 and 70 response rates of 65%, 52% and 24%, respectively, compared to placebo responses of 13%, 7% and 3% respectively, at 6 months ($p<0.01$).

The results of the components of the ACR response criteria for Studies RA-II and RA-III are shown in Table 3. ACR response rates and improvement in all components of ACR response were maintained to week

104. Over the 2 years in Study RA-III, 20% of HUMIRA patients receiving 40 mg every other week (EOW) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period. ACR responses were maintained in similar proportions of patients for up to 5 years with continuous HUMIRA treatment in the open-label portion of Study RA-III.

Table 3. Components of ACR Response in Studies RA-II and RA-III

	Study RA-II				**Study RA-III**			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen joints (0-66)	19	16	18	10*	17	11	18	5*
Physician global assessment[b]	7.0	6.1	6.6	3.7*	6.3	3.5	6.5	2.0*
Patient global assessment[b]	7.5	6.3	7.5	4.5*	5.4	3.9	5.2	2.0*
Pain[b]	7.3	6.1	7.3	4.1*	6.0	3.8	5.8	2.1*
Disability index (HAQ)[c]	2.0	1.9	1.9	1.5*	1.5	1.3	1.5	0.8*
CRP (mg/dL)	3.9	4.3	4.6	1.8*	1.0	0.9	1.0	0.4*

[a] 40 mg HUMIRA administered every other week

[b] Visual analogue scale; 0 = best, 10 = worst

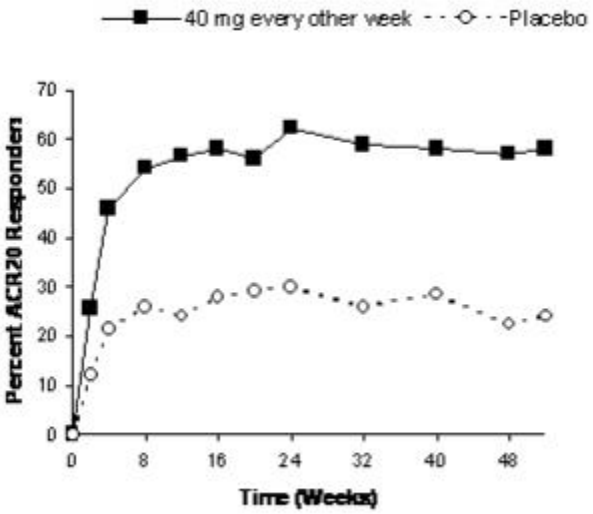
[c] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

* $p<0.001$, HUMIRA *vs.* placebo, based on mean change from baseline

The time course of ACR 20 response for Study RA-III is shown in Figure 1.

In Study RA-III, 85% of patients with ACR 20 responses at week 24 maintained the response at 52 weeks. The time course of ACR 20 response for Study RA-I and Study RA-II were similar.

Figure 1. Study RA-III ACR 20 Responses over 52 Weeks



In Study RA-IV, 53% of patients treated with HUMIRA 40 mg every other week plus standard of care had an ACR 20 response at week 24 compared to 35% on placebo plus standard of care ($p<0.001$). No unique adverse reactions related to the combination of HUMIRA (adalimumab) and other DMARDs were observed.

In Study RA-V with MTX naïve patients with recent onset RA, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 4).

Table 4. ACR Response in Study RA-V (Percent of Patients)

Response	**MTX[b] N=257**	**HUMIRA[c] N=274**	**HUMIRA/MTX N=268**
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period
[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20
$p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response
[c] $p<0.001$, HUMIRA/MTX *vs.* HUMIRA

At Week 52, all individual components of the ACR response criteria for Study RA-V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study RA-III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 5. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 5. Radiographic Mean Changes Over 12 Months in Study RA-III

	Placebo/MTX	HUMIRA/MTX 40 mg every other week	Placebo/MTX-HUMIRA/MTX (95% Confidence Interval*)	P-value**
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	<0.001
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	<0.001
JSN score	1.0	0.1	0.9 (0.3, 1.4)	0.002

*95% confidence intervals for the differences in change scores between MTX and HUMIRA.
**Based on rank analysis

In the open-label extension of Study RA-III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less. Fifty-five percent (55%) of patients originally treated with 40 mg HUMIRA every other week have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage with 50% showing no progression of structural damage defined by a change in the TSS of zero or less.

In Study RA-V, structural joint damage was assessed as in Study RA-III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6. Radiographic Mean Change* in Study RA-V

		MTX[a] N=257	**HUMIRA[a,b] N=274**	**HUMIRA/MTX N=268**
52 Weeks	Total Sharp score	5.7 (4.2, 7.3)	3.0 (1.7, 4.3)	1.3 (0.5, 2.1)
	Erosion score	3.7 (2.7, 4.8)	1.7 (1.0, 2.4)	0.8 (0.4, 1.2)
	JSN score	2.0 (1.2, 2.8)	1.3 (0.5, 2.1)	0.5 (0.0, 1.0)
104 Weeks	Total Sharp score	10.4 (7.7, 13.2)	5.5 (3.6, 7.4)	1.9 (0.9, 2.9)
	Erosion score	6.4 (4.6, 8.2)	3.0 (2.0, 4.0)	1.0 (0.4, 1.6)
	JSN score	4.1 (2.7, 5.4)	2.6 (1.5, 3.7)	0.9 (0.3, 1.5)

* mean (95% confidence interval)
[a] p<0.001, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks
[b] p<0.01, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

In studies RA-I through IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF

36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study RA-III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX ($p<0.001$) patients. Sixty-three percent of HUMIRA-treated patients achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study. Eighty-two percent of these patients maintained that improvement through week 104 and a similar proportion of patients maintained this response through week 260 (5 years) of open-label treatment. Mean improvement in the SF-36 was maintained through the end of measurement at week 156 (3 years).

In Study RA-V, the HAQ-DI and the physical component of the SF-36 showed greater improvement ($p<0.001$) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

14.2 Juvenile Idiopathic Arthritis

The safety and efficacy of HUMIRA were assessed in a multicenter, randomized, withdrawal, double-blind, parallel-group study in 171 children (4 to 17 years of age) with polyarticular juvenile idiopathic arthritis (JIA). In the study, the patients were stratified into two groups: MTX-treated or non-MTX-treated. All subjects had to show signs of active moderate or severe disease despite previous treatment with NSAIDs, analgesics, corticosteroids, or DMARDS. Subjects who received prior treatment with any biologic DMARDS were excluded from the study.

The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, HUMIRA was administered based on body surface area at a dose of 24 mg/m^2 up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of HUMIRA SC every other week if their weight was less than 30 kg and with 40 mg of HUMIRA SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum).

Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either HUMIRA or placebo every other week for 32 weeks or until disease flare. Disease flare was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase).

Clinical Response

At the end of the 16-week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non-MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients who

received HUMIRA experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with HUMIRA continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received HUMIRA throughout the study.

14.3 Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis (PsA). Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg HUMIRA was administered every other week.

Study PsA-I enrolled 313 adult patients with moderately to severely active PsA (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of plaque psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric PsA (N=77); or (5) AS-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with PsA who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks in the ongoing open-label study. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the HUMIRA group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) ($p<0.001$). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 7. ACR Response in Study PsA-I (Percent of Patients)

	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%
* $p<0.001$ for all comparisons between HUMIRA and placebo		

Table 8. Components of Disease Activity in Study PsA-I

	Placebo N=162		HUMIRA* N=151	
Parameter: median	Baseline	24 weeks	Baseline	24 weeks
Number of tender joints[a]	23.0	17.0	20.0	5.0
Number of swollen joints[b]	11.0	9.0	11.0	3.0
Physician global assessment[c]	53.0	49.0	55.0	16.0
Patient global assessment[c]	49.5	49.0	48.0	20.0
Pain[c]	49.0	49.0	54.0	20.0
Disability index (HAQ)[d]	1.0	0.9	1.0	0.4
CRP (mg/dL)[e]	0.8	0.7	0.8	0.2

* p<0.001 for HUMIRA *vs.* placebo comparisons based on median changes

[a] Scale 0-78

[b] Scale 0-76

[c] Visual analog scale; 0=best, 100=worst

[d] Disability Index of the Health Assessment Questionnaire; 0=best, 3=worst; measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

[e] Normal range: 0-0.287 mg/dL

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by ≥3 tender joints and ≥3 swollen joints at enrollment.

Radiographic Response

Radiographic changes were assessed in the PsA studies. Radiographs of hands, wrists, and feet were obtained at baseline and Week 24 during the double-blind period when patients were on HUMIRA or placebo and at Week 48 when all patients were on open-label HUMIRA. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used by readers blinded to treatment group to assess the radiographs.

HUMIRA-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks (see Table 9).

Table 9. Change in Modified Total Sharp Score in Psoriatic Arthritis

	Placebo N=141	**HUMIRA N=133**	
	Week 24	Week 24	Week 48
Baseline mean	22.1	23.4	23.4
Mean Change ± SD	0.9 ± 3.1	-0.1 ± 1.7	-0.2 ± 4.9*

* <0.001 for the difference between HUMIRA, Week 48 and Placebo, Week 24 (primary analysis)

Physical Function Response

In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of HUMIRA every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24

respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively). At Weeks 12 and 24, patients treated with HUMIRA showed greater improvement from baseline in the SF-36 Physical Component Summary score compared to patients treated with placebo, and no worsening in the SF-36 Mental Component Summary score. Improvement in physical function based on the HAQ-DI was maintained for up to 84 weeks through the open-label portion of the study.

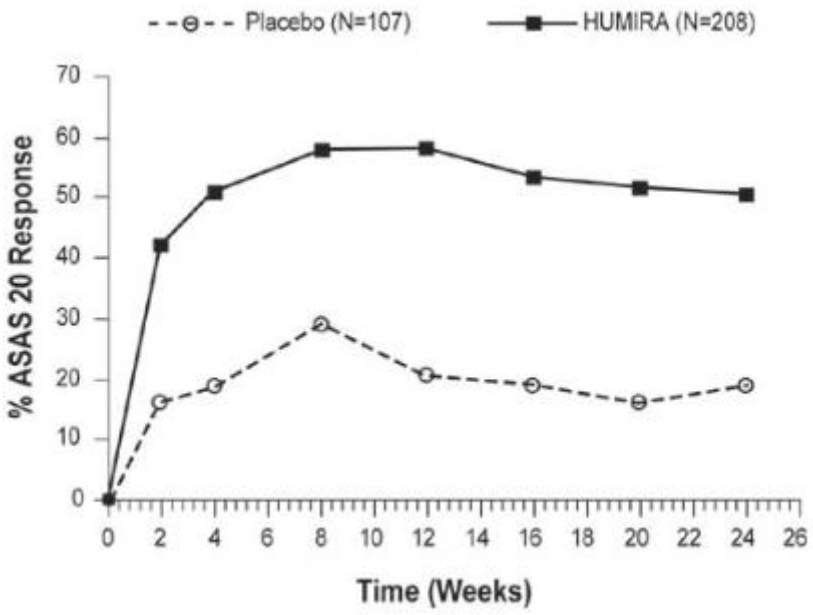
14.4 Ankylosing Spondylitis

The safety and efficacy of HUMIRA 40 mg every other week was assessed in 315 adult patients in a randomized, 24 week double-blind, placebo-controlled study in patients with active ankylosing spondylitis (AS) who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Active AS was defined as patients who fulfilled at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, and (3) morning stiffness ≥ 1 hour. The blinded period was followed by an open-label period during which patients received HUMIRA 40 mg every other week subcutaneously for up to an additional 28 weeks.

Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 2 and Table 10.

Responses of patients with total spinal ankylosis (n=11) were similar to those without total ankylosis.

Figure 2. ASAS 20 Response By Visit, Study AS-I



At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving HUMIRA, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p < 0.001$). Similar responses were seen at Week 24 and were sustained in patients receiving open-label HUMIRA for up to 52 weeks.

A greater proportion of patients treated with HUMIRA (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

Table 10. Components of Ankylosing Spondylitis Disease Activity

	Placebo N=107		HUMIRA N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a*]	65	60	63	38
Total back pain*	67	58	65	37
Inflammation[b*]	6.7	5.6	6.7	3.6
BASFI[c*]	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8
CRP[f*]	2.2	2.0	1.8	0.6

[a] Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"
[b] mean of questions 5 and 6 of BASDAI (defined in 'd')
[c] Bath Ankylosing Spondylitis Functional Index
[d] Bath Ankylosing Spondylitis Disease Activity Index
[e] Bath Ankylosing Spondylitis Metrology Index
[f] C-Reactive Protein (mg/dL)
* statistically significant for comparisons between HUMIRA and placebo at Week 24

A second randomized, multicenter, double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results.

Patients treated with HUMIRA achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 *vs.* -1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 *vs.* 1.9) compared to placebo-treated patients at Week 24.

14.5 Crohn's Disease

The safety and efficacy of multiple doses of HUMIRA were assessed in adult patients with moderately to severely active Crohn's disease, CD, (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomized, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted, and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. In Study CD-I, 299 TNF-blocker naïve patients were randomized to one of four treatment groups: the placebo group received

placebo at Weeks 0 and 2, the 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the 80/40 group received 80 mg at Week 0 and 40 mg at Week 2, and the 40/20 group received 40 mg at Week 0 and 20 mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, Study CD-II, 325 patients who had lost response to, or were intolerant to, previous infliximab therapy were randomized to receive either 160 mg HUMIRA at Week 0 and 80 mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in Study CD-III. In this study, 854 patients with active disease received open-label HUMIRA, 80 mg at week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg HUMIRA every other week, 40 mg HUMIRA every week, or placebo. The total study duration was 56 weeks. Patients in clinical response (decrease in CDAI ≥70) at Week 4 were stratified and analyzed separately from those not in clinical response at Week 4.

Induction of Clinical Remission

A greater percentage of the patients treated with 160/80 mg HUMIRA achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II) (see Table 11).

Table 11. Induction of Clinical Remission in Studies CD-I and CD-II (Percent of Patients)

	CD-I		CD-II	
	Placebo N=74	**HUMIRA 160/80 mg N=76**	**Placebo N=166**	**HUMIRA 160/80 mg N=159**
Week 4				
Clinical remission	12%	36%*	7%	21%*
Clinical response	34%	58%**	34%	52%**

Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points.
* p<0.001 for HUMIRA *vs.* placebo pairwise comparison of proportions
** p<0.01 for HUMIRA *vs.* placebo pairwise comparison of proportions

Maintenance of Clinical Remission

In Study CD-III at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the HUMIRA 40 mg every other week maintenance group compared to patients in the placebo maintenance group (see Table 12). The group that received HUMIRA therapy every week did not demonstrate significantly higher remission rates compared to the group that received HUMIRA every other week.

Table 12. Maintenance of Clinical Remission in CD-III (Percent of Patients)

	Placebo	40 mg HUMIRA every other week
	N=170	N=172
Week 26		
Clinical remission	17%	40%*
Clinical response	28%	54%*
Week 56		
Clinical remission	12%	36%*
Clinical response	18%	43%*
Clinical remission is CDAI score < 150; clinical response is decrease in CDAI of at least 70 points. *p<0.001 for HUMIRA vs. placebo pairwise comparisons of proportions		

Of those in response at Week 4 who attained remission during the study, patients in the HUMIRA every other week group maintained remission for a longer time than patients in the placebo maintenance group. Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

14.6 Ulcerative Colitis

The safety and efficacy of HUMIRA were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a 12 point scale, with an endoscopy subscore of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, double-blind, placebo-controlled clinical studies (Studies UC-I and UC-II). Both studies enrolled TNF-blocker naïve patients, but Study UC-II also allowed entry of patients who lost response to or were intolerant to TNF-blockers. Forty percent (40%) of patients enrolled in Study UC-II had previously used another TNF-blocker.

Concomitant stable doses of aminosalicylates and immunosuppressants were permitted. In Studies UC-I and II, patients were receiving aminosalicylates (69%), corticosteroids (59%) and/or azathioprine or 6-MP (37%) at baseline. In both studies, 92% of patients received at least one of these medications.

Induction of clinical remission (defined as Mayo score ≤ 2 with no individual subscores > 1) at Week 8 was evaluated in both studies. Clinical remission at Week 52 and sustained clinical remission (defined as clinical remission at both Weeks 8 and 52) were evaluated in Study UC-II.

In Study UC-I, 390 TNF-blocker naïve patients were randomized to one of three treatment groups for the primary efficacy analysis. The placebo group received placebo at Weeks 0, 2, 4 and 6. The 160/80 group received 160 mg HUMIRA at Week 0 and 80 mg at Week 2, and the 80/40 group received 80 mg HUMIRA at Week 0 and 40 mg at Week 2. After Week 2, patients in both HUMIRA treatment groups received 40 mg every other week (eow).

In Study UC-II, 518 patients were randomized to receive either HUMIRA 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4 through Week 50, or placebo starting at Week 0 and eow through Week 50. Corticosteroid taper was permitted starting at Week 8.

In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the patients treated with 160/80 mg of HUMIRA compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52) (Table 13).

Table 13. Induction of Clinical Remission in Studies UC-I and UC-II and Sustained Clinical Remission in Study UC-II (Percent of Patients)

	Study UC-I			Study UC-II		
	Placebo N=130	**HUMIRA 160/80 mg N=130**	**Treatment Difference (95% CI)**	**Placebo N=246**	**HUMIRA 160/80 mg N=248**	**Treatment Difference (95% CI)**
Induction of Clinical Remission (Clinical Remission at Week 8)	9.2%	18.5%	9.3%* (0.9%, 17.6%)	9.3%	16.5%	7.2%* (1.2%, 12.9%)
Sustained Clinical Remission (Clinical Remission at both Weeks 8 and 52)	N/A	N/A	N/A	4.1%	8.5%	4.4%* (0.1%, 8.6%)

Clinical remission is defined as Mayo score ≤ 2 with no individual subscores > 1.
CI=Confidence interval
* p<0.05 for HUMIRA *vs.* placebo pairwise comparison of proportions

In Study UC-I, there was no statistically significant difference in clinical remission observed between the HUMIRA 80/40 mg group and the placebo group at Week 8.

In Study UC-II, 17.3% (43/248) in the HUMIRA group were in clinical remission at Week 52 compared to 8.5% (21/246) in the placebo group (treatment difference: 8.8%; 95% confidence interval (CI): [2.8%, 14.5%]; p<0.05).

In the subgroup of patients in Study UC-II with prior TNF-blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population. The subgroup of patients with prior TNF-blocker use achieved induction of clinical remission at 9% (9/98) in the HUMIRA group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the HUMIRA group versus 1% (1/101) in the placebo group. In the subgroup of patients with prior TNF-blocker use, 10% (10/98) were in clinical remission at Week 52 in the HUMIRA group versus 3% (3/101) in the placebo group.

14.7 Plaque Psoriasis

The safety and efficacy of HUMIRA were assessed in randomized, double-blind, placebo-controlled studies in 1696 adult patients with moderate to severe chronic plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy.

Study Ps-I evaluated 1212 patients with chronic Ps with ≥10% body surface area (BSA) involvement, Physician's Global Assessment (PGA) of at least moderate disease severity, and Psoriasis Area and Severity Index (PASI) ≥12 within three treatment periods. In period A, patients received placebo or HUMIRA at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score

improvement of at least 75% relative to baseline, entered period B and received open-label 40 mg HUMIRA every other week. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in period A were re-randomized in period C to receive 40 mg HUMIRA every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 19 and the baseline Physician's Global Assessment score ranged from "moderate" (53%) to "severe" (41%) to "very severe" (6%).

Study Ps-II evaluated 99 patients randomized to HUMIRA and 48 patients randomized to placebo with chronic plaque psoriasis with ≥10% BSA involvement and PASI ≥12. Patients received placebo, or an initial dose of 80 mg HUMIRA at Week 0 followed by 40 mg every other week starting at Week 1 for 16 weeks. Across all treatment groups the mean baseline PASI score was 21 and the baseline PGA score ranged from "moderate" (41%) to "severe" (51%) to "very severe" (8%).

Studies Ps-I and II evaluated the proportion of patients who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 (see Table 14 and 15).

Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52.

Table 14. Efficacy Results at 16 Weeks in Study Ps-I Number of Patients (%)

	HUMIRA 40 mg every other week	Placebo
	N = 814	N = 398
PGA: Clear or minimal*	506 (62%)	17 (4%)
PASI 75	578 (71%)	26 (7%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Table 15. Efficacy Results at 16 Weeks in Study Ps-II Number of Patients (%)

	HUMIRA 40 mg every other week	Placebo
	N = 99	N = 48
PGA: Clear or minimal*	70 (71%)	5 (10%)
PASI 75	77 (78%)	9 (19%)
* Clear = no plaque elevation, no scale, plus or minus hyperpigmentation or diffuse pink or red coloration Minimal = possible but difficult to ascertain whether there is slight elevation of plaque above normal skin, plus or minus surface dryness with some white coloration, plus or minus up to red coloration		

Additionally, in Study Ps-I, subjects on HUMIRA who maintained a PASI 75 were re-randomized to HUMIRA (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with HUMIRA, more patients on HUMIRA maintained efficacy when compared to subjects who were re-randomized to placebo based on maintenance of PGA of "clear" or "minimal" disease (68% *vs.* 28%) or a PASI 75 (79% *vs.* 43%).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA "moderate" or worse) was approximately 5 months. During the withdrawal period, no subject experienced transformation to either pustular or erythrodermic

psoriasis. A total of 178 subjects who relapsed re-initiated treatment with 80 mg of HUMIRA, then 40 mg eow beginning at week 1. At week 16, 69% (123/178) of subjects had a response of PGA "clear" or "minimal".

15 REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 11 Registries, 1993-2001.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied in prefilled syringes as a preservative-free, sterile solution for subcutaneous administration. The following packaging configurations are available.

- **HUMIRA Pen Carton**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-02.

- **HUMIRA Pen – Crohn's Disease/Ulcerative Colitis Starter Package**

HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Crohn's Disease/Ulcerative Colitis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-06.

- **HUMIRA Pen – Psoriasis Starter Package**

HUMIRA is dispensed in a carton containing 4 alcohol preps and 4 dose trays (Psoriasis Starter Package). Each dose tray consists of a single-use pen, containing a 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-4339-07.

- **Prefilled Syringe Carton – 40 mg**

HUMIRA is dispensed in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 40 mg (0.8 mL) of HUMIRA. The NDC number is 0074-3799-02.

- **Pediatric Prefilled Syringe Carton - 20 mg**

HUMIRA is supplied for pediatric use only in a carton containing two alcohol preps and two dose trays. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle, providing 20 mg (0.4 mL) of HUMIRA. The NDC number is 0074-9374-02.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. When traveling, store HUMIRA in a cool carrier with an ice pack. Protect the prefilled syringe from exposure to light. Store in original carton until time of administration.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

17.1 Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

17.2 Instruction on Injection Technique

Inform patients that the first injection is to be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, instruct them in injection techniques and assess their ability to inject subcutaneously to ensure the proper administration of HUMIRA *[see Instructions for Use]*.

For patients who will use the HUMIRA Pen, tell them that they:

- Will hear a **loud 'click'** when the plum-colored activator button is pressed. The loud click means the **start** of the injection.

- Must keep holding the HUMIRA Pen against their squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds.
- Will know that the injection has finished when the yellow marker fully appears in the window view and stops moving.

Instruct patients to dispose of their used needles and syringes or used Pen in a FDA-cleared sharps disposal container immediately after use. **Instruct patients not to dispose of loose needles and syringes or Pen in their household trash.** Instruct patients that if they do not have a FDA-cleared sharps disposal container, they may use a household container that is made of a heavy-duty plastic, can be closed with a tight-fitting and puncture-resistant lid without sharps being able to come out, upright and stable during use, leak-resistant, and properly labeled to warn of hazardous waste inside the container.

Instruct patients that when their sharps disposal container is almost full, they will need to follow their community guidelines for the correct way to dispose of their sharps disposal container. Instruct patients that there may be state or local laws regarding disposal of used needles and syringes. Refer patients to the FDA's website at http://www.fda.gov/safesharpsdisposal for more information about safe sharps disposal, and for specific information about sharps disposal in the state that they live in.

Instruct patients not to dispose of their used sharps disposal container in their household trash unless their community guidelines permit this. Instruct patients not to recycle their used sharps disposal container.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

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MEDICATION GUIDE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

injection

Read the Medication Guide that comes with HUMIRA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about HUMIRA?

HUMIRA is a medicine that affects your immune system. HUMIRA can lower the ability of your immune system to fight infections. **Serious infections have happened in people taking HUMIRA. These serious**

infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.

- Your doctor should test you for TB before starting HUMIRA.
- Your doctor should check you closely for signs and symptoms of TB during treatment with HUMIRA.

You should not start taking HUMIRA if you have any kind of infection unless your doctor says it is okay.

Before starting HUMIRA, tell your doctor if you:

- think you have an infection or have symptoms of infection such as:

• fever, sweats, or chills	• warm, red, or painful skin or sores on your body	
• muscle aches	• diarrhea or stomach pain	
• cough	• burning when you urinate or urinate more often than normal	
• shortness of breath	• feel very tired	
• blood in phlegm		
• weight loss		

- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes
- have TB, or have been in close contact with someone with TB
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use HUMIRA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B
- use the medicine ORENCIA® (abatacept), KINERET® (anakinra), RITUXAN® (rituximab), IMURAN® (azathioprine), or PURINETHOL® (6–mercaptopurine, 6-MP).
- are scheduled to have major surgery

After starting HUMIRA, call your doctor right away if you have an infection, or any sign of an infection.

HUMIRA can make you more likely to get infections or make any infection that you may have worse.

Cancer

- For children and adults taking TNF-blockers, including HUMIRA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children, teenagers, and young adults using TNF-blockers.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers including HUMIRA your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn't heal.
- Some people receiving TNF blockers including HUMIRA developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6–MP).

See the "What are the possible side effects of HUMIRA?" section.

What is HUMIRA?

HUMIRA is a medicine called a Tumor Necrosis Factor (TNF) blocker. HUMIRA is used:

- To reduce the signs and symptoms of:
    - **moderate to severe rheumatoid arthritis (RA) in adults.** HUMIRA can be used alone, with methotrexate, or with certain other medicines.
    - **moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children** 4 years and older. HUMIRA can be used alone, with methotrexate, or with certain other medicines.
    - **psoriatic arthritis (PsA) in adults.** HUMIRA can be used alone or with certain other medicines.
    - **ankylosing spondylitis (AS) in adults.**
    - **moderate to severe Crohn's disease (CD) in adults** when other treatments have not worked well enough.
- In adults, to help get **moderate to severe ulcerative colitis (UC)** under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if HUMIRA is effective in people who stopped responding to or could not tolerate TNF-blocker medicines.
- **To treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps) in adults** who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

What should I tell my doctor before taking HUMIRA?

HUMIRA may not be right for you. Before starting HUMIRA, tell your doctor about all of your health conditions, including if you:

- have an infection. See **"What is the most important information I should know about HUMIRA?"**
- have or have had cancer.
- have any numbness or tingling or have a disease that affects your nervous system such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using HUMIRA. Children with juvenile idiopathic arthritis should be brought up to date with all vaccines before starting HUMIRA.
- are allergic to rubber or latex. The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.
- are allergic to HUMIRA or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in HUMIRA.
- are pregnant or planning to become pregnant. It is not known if HUMIRA will harm your unborn baby. HUMIRA should only be used during a pregnancy if needed.
  Pregnancy Registry: Abbott Laboratories has a registry for pregnant women who take HUMIRA. The purpose of this registry is to check the health of the pregnant mother and her child. Talk to your doctor if you are pregnant and contact the registry at 1–877–311–8972.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use HUMIRA. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you use:

- ORENCIA® (abatacept), KINERET® (anakinra), REMICADE® (infliximab), ENBREL® (etanercept), CIMZIA® (certolizumab pegol) or SIMPONI® (golimumab), because you should not use HUMIRA while you are also taking one of these medicines.
- RITUXAN® (rituximab). Your doctor may not want to give you HUMIRA if you have received RITUXAN® (rituximab) recently.
- IMURAN® (azathioprine) or PURINETHOL® (6–mercaptopurine, 6-MP).

Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take HUMIRA?

- HUMIRA is given by an injection under the skin. Your doctor will tell you how often to take an injection of HUMIRA. This is based on your condition to be treated. **Do not inject HUMIRA more often than you were prescribed.**
- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject HUMIRA.
- Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or 1-800-4HUMIRA (1-800-448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection after he/she has been shown how to prepare and inject HUMIRA.
- **Do not** try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA.
- Do not miss any doses of HUMIRA unless your doctor says it is okay. If you forget to take HUMIRA, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. In case you are not sure when to inject HUMIRA, call your doctor or pharmacist.
- If you take more HUMIRA than you were told to take, call your doctor.

What are the possible side effects of HUMIRA?

HUMIRA can cause serious side effects, including:

See "What is the most important information I should know about HUMIRA?"

- **Serious Infections.**

  Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with HUMIRA and during treatment with HUMIRA. Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking HUMIRA. People who had a negative TB skin test before receiving HUMIRA have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking HUMIRA:

  - cough that does not go away
  - low grade fever
  - weight loss
  - loss of body fat and muscle (wasting)
- **Hepatitis B infection in people who carry the virus in their blood.**

If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use HUMIRA. Your doctor should do blood tests before you start treatment, while you are using HUMIRA, and for several months after you stop treatment with HUMIRA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

- muscle aches
- feel very tired
- dark urine
- skin or eyes look yellow
- little or no appetite
- vomiting
- clay-colored bowel movements
- fever
- chills
- stomach discomfort
- skin rash

- **Allergic reactions.** Allergic reactions can happen in people who use HUMIRA. Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:
    - hives
    - swelling of your face, eyes, lips or mouth
    - trouble breathing
- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.
- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have. Call your doctor right away** if you get new worsening symptoms of heart failure while taking HUMIRA, including:
    - shortness of breath
    - swelling of your ankles or feet
    - sudden weight gain.
- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may improve when you stop HUMIRA.
- **Liver Problems.** Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
    - feel very tired
    - skin or eyes look yellow
    - poor appetite or vomiting

- pain on the right side of your stomach (abdomen)

- **Psoriasis.** Some people using HUMIRA had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with HUMIRA.

Call your doctor or get medical care right away if you develop any of the above symptoms. Your treatment with HUMIRA may be stopped.

Common side effects with HUMIRA include:

- injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
- upper respiratory infections (including sinus infections)
- headaches
- rash
- nausea

These are not all the possible side effects with HUMIRA. Tell your doctor if you have any side effect that bothers you or that does not go away. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store HUMIRA?

- Store HUMIRA in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, Pen or prefilled syringe.
- Do not use a Pen or prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

General information about HUMIRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HUMIRA for a condition for which it was not prescribed. Do not give HUMIRA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about HUMIRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about HUMIRA that was written for healthcare professionals.

For more information go to www.HUMIRA.com or you can enroll in a patient support program by calling 1-800-4HUMIRA (1-800-448-6472).

What are the ingredients in HUMIRA?

Active ingredient: adalimumab

Inactive ingredients: sodium chloride, monobasic sodium phosphate dihydrate, dibasic sodium phosphate dihydrate, sodium citrate, citric acid monohydrate, mannitol, polysorbate 80, and Water for Injection. Sodium hydroxide is added as necessary to adjust pH.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Content revised 09/2012

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

SINGLE-USE PEN

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. Call your healthcare provider if you or your caregiver has any questions about the right way to inject HUMIRA.

IMPORTANT:

- Do not use HUMIRA if frozen, even if it has been thawed.
- The HUMIRA Pen contains glass. Do not drop or crush the Pen because the glass inside may break.

- Do not remove the gray cap or the plum-colored cap until right before your injection.
- When the plum-colored button on the HUMIRA Pen is pressed to give your dose of HUMIRA, you will hear a loud "click" sound.
    - You must practice injecting HUMIRA with your doctor or nurse so that you are not startled by this click when you start giving yourself the injections at home.
    - The loud click sound means the start of the injection.
    - You will know that the injection has finished when the yellow marker appears fully in the window view and stops moving.

See the section below called **"Prepare the HUMIRA Pen"**.

How should I store HUMIRA?

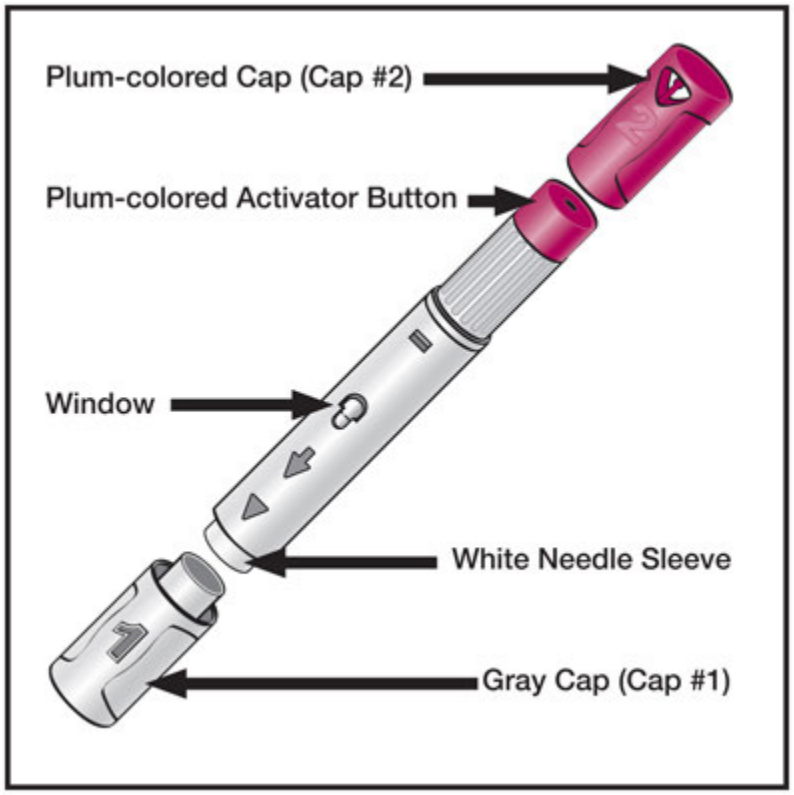
- Store HUMIRA in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray, and Pen.
- Do not use a Pen if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

Gather the Supplies for Your Injection

- You will need the following supplies for your injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
    - 1 alcohol swab
    - 1 cotton ball or gauze pad (not included in your HUMIRA carton)
    - 1 HUMIRA Pen (See Figure A)
    - 1 FDA-cleared sharps disposal container for HUMIRA Pen disposal (not included in your HUMIRA carton)

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist. The diagram below shows what the HUMIRA Pen looks like. See Figure A.

Figure A



Check the carton, dose tray, and HUMIRA Pen.

1. Make sure the name HUMIRA appears on the carton, dose tray, and HUMIRA Pen label.

2. **Do not** use and call your doctor or pharmacist if:

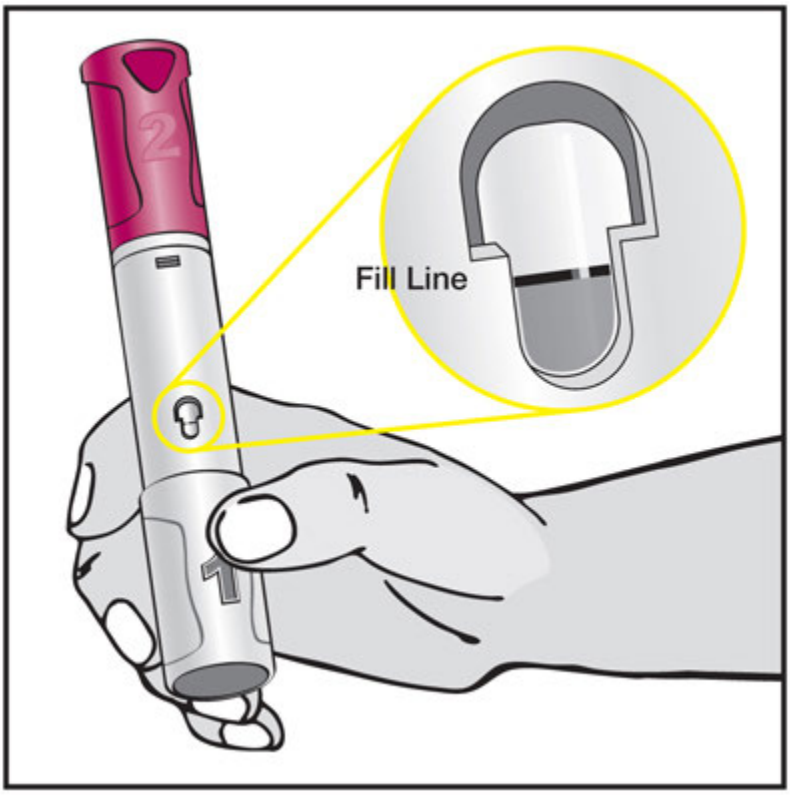
- you drop or crush your HUMIRA Pen.
- the seals on the top or bottom of the carton are broken or missing.
- the expiration date on the carton, dose tray, and Pen has passed.
- the HUMIRA Pen has been frozen or left in direct sunlight. See the section: **"How should I store HUMIRA?"** at the beginning of these Instructions For Use.

3. Hold the Pen with the gray cap (Cap # 1) pointed down.

4. Make sure the amount of liquid in the Pen is at the fill line or close to the fill line seen through the window. This is the full dose of HUMIRA that you will inject. See Figure B.

5. If the Pen does not have the full amount of liquid, **do not use that Pen**. Call your pharmacist.

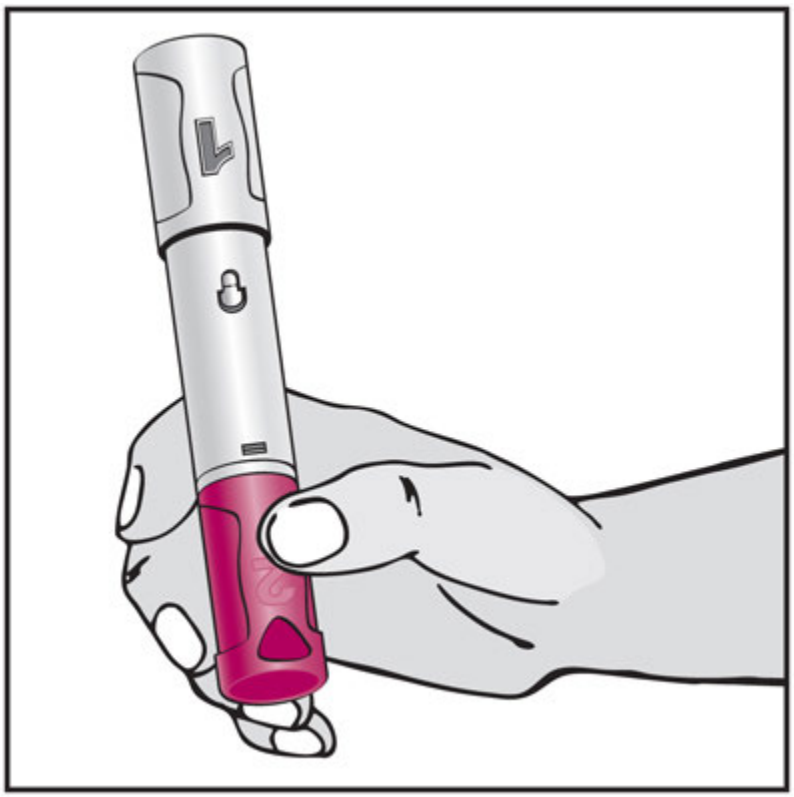
Figure B



6. Turn the Pen over and hold the Pen with the gray cap (Cap # 1) pointed up. See Figure C.

7. Check the solution through the windows on the side of the Pen to make sure the liquid is clear and colorless. **Do not use** your HUMIRA Pen if the liquid is cloudy, discolored, or if it has flakes or particles in it. Call your pharmacist. It is normal to see one or more bubbles in the window.

Figure C



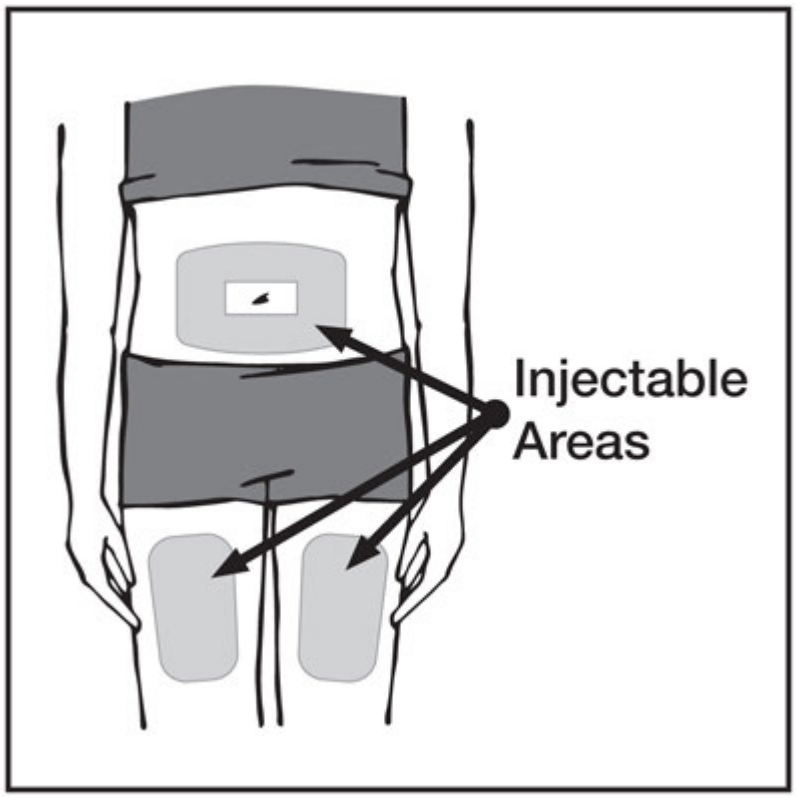
Choose the Injection Site

8. Wash and dry your hands well.

9. Choose an injection site on:

- the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure D.

Figure D



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject HUMIRA into skin that is:
    - sore (tender)
    - bruised
    - red
    - hard
    - scarred or where you have stretch marks
- If you have psoriasis, **do not** inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

10. Wipe the injection site with an alcohol prep (swab) using a circular motion.

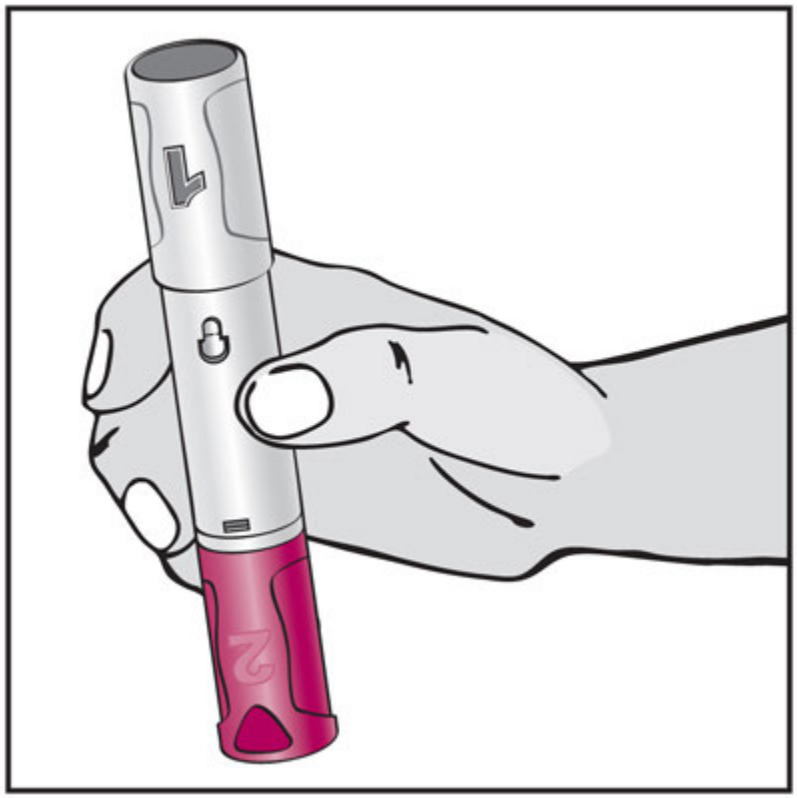
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

Preparing the HUMIRA Pen

11. **Do not remove the gray cap (Cap # 1) or the plum-colored cap (Cap # 2) until right before your injection.**

12. Hold the middle of the Pen (gray body) with one hand so that you are not touching the gray cap (Cap # 1) or the plum-colored cap (Cap # 2). Turn the Pen so that the gray cap (Cap # 1) is pointing up. See Figure E.

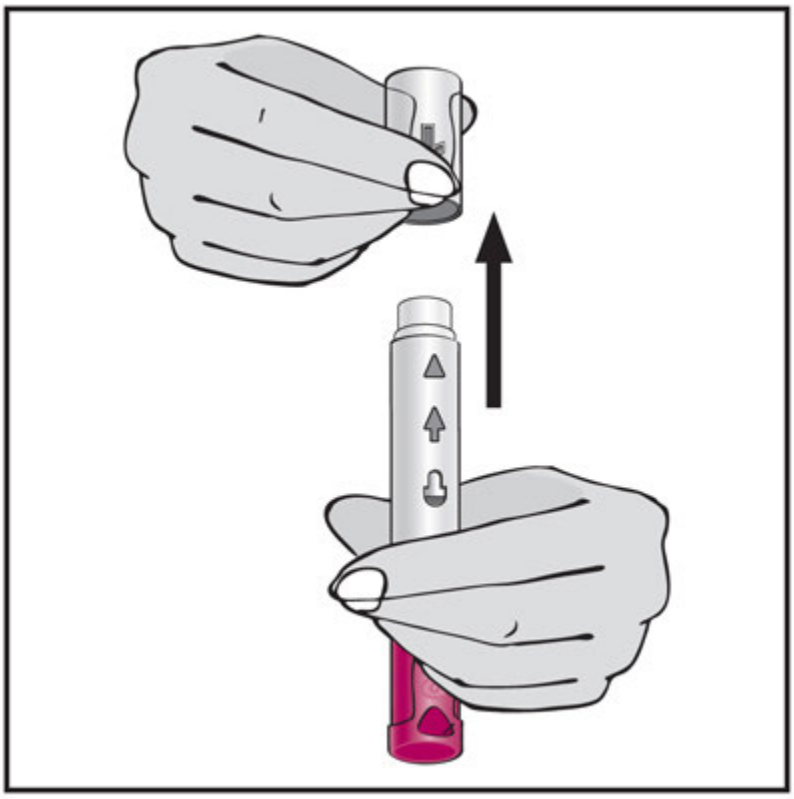
Figure E



13. With your other hand, pull the gray cap (Cap # 1) straight off (do not twist the cap). Make sure the small gray needle cover of the syringe has come off with the gray cap (Cap # 1). See Figure F.

14. Throw away the gray cap (Cap # 1).

Figure F



- **Do not** put the gray cap (Cap # 1) back on the Pen. Putting the gray cap (Cap # 1) back on may damage the needle.
- The white needle sleeve, which covers the needle, can now be seen.
- **Do not** touch the needle with your fingers or let the needle touch anything.
- You may see a few drops of liquid come out of the needle. This is normal.

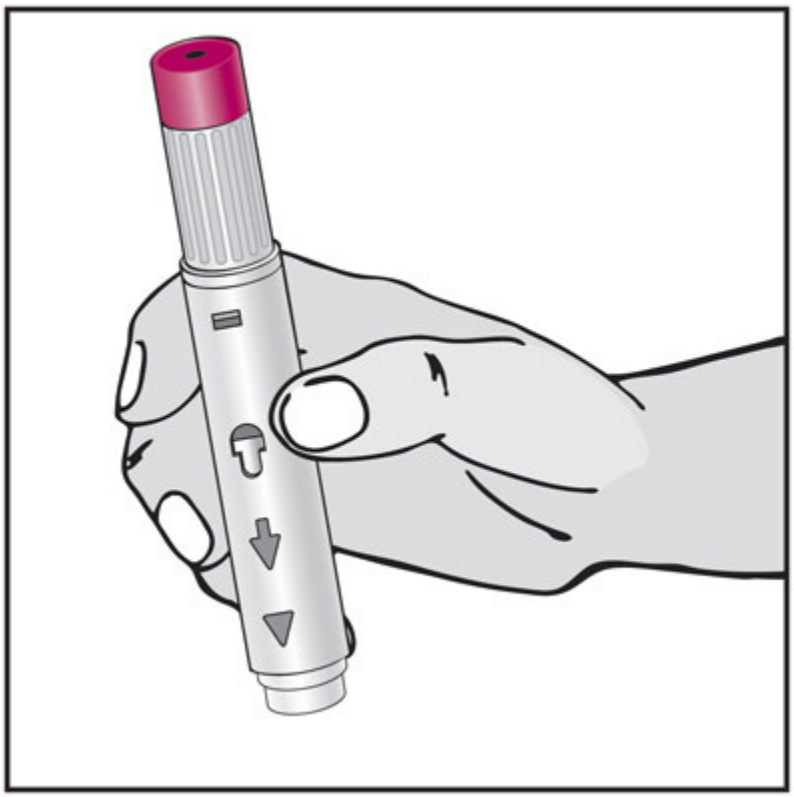
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- Do not put the plum-colored cap (Cap # 2) back on the Pen because it could cause medicine to come out of the syringe.

The plum-colored activator button:

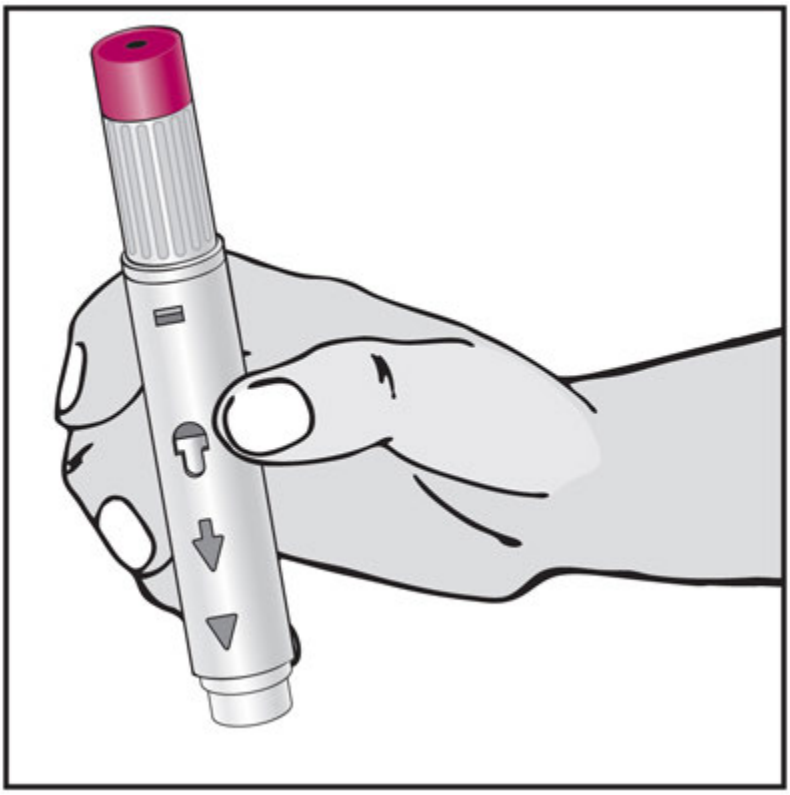
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

Figure G



- **Do not** press the plum-colored activator button until you are ready to inject HUMIRA. Pressing the plum-colored activator button will release the medicine from the Pen.
- Hold the Pen so that you can see the window. See Figure H. It is normal to see one or more bubbles in the window.

Figure H



Position the Pen and Inject HUMIRA

16. Position the Pen:

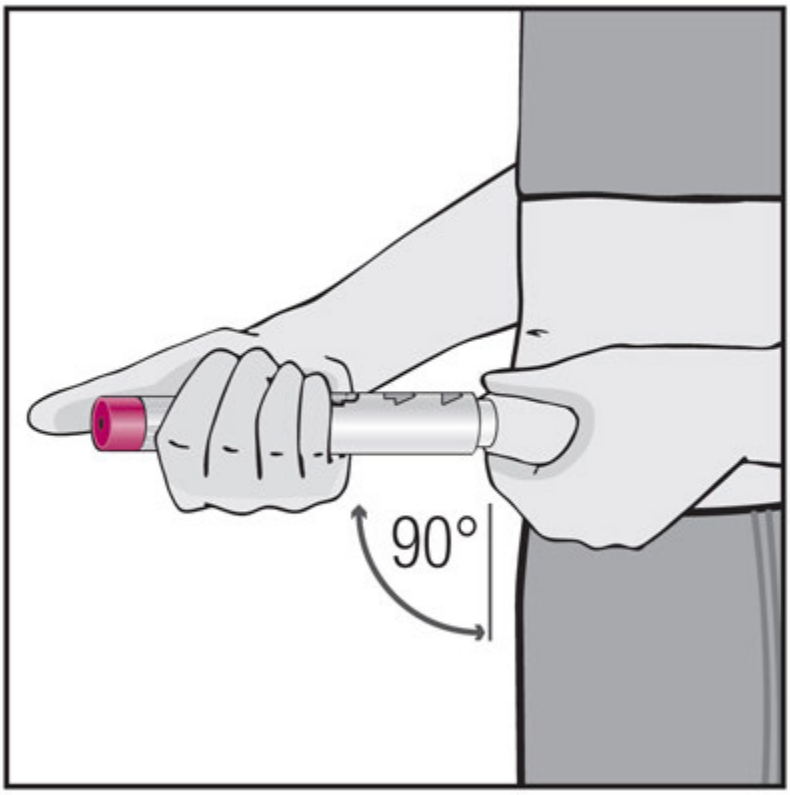
- Gently squeeze the area of the cleaned skin and hold it firmly. See Figure I. You will inject into this raised area of skin.

Figure I



17. Place the white end of the Pen straight (at a 90º angle) and flat against the raised area of your skin that you are squeezing. Place the Pen so that it will not inject the needle into your fingers that are holding the raised skin. See Figure J.

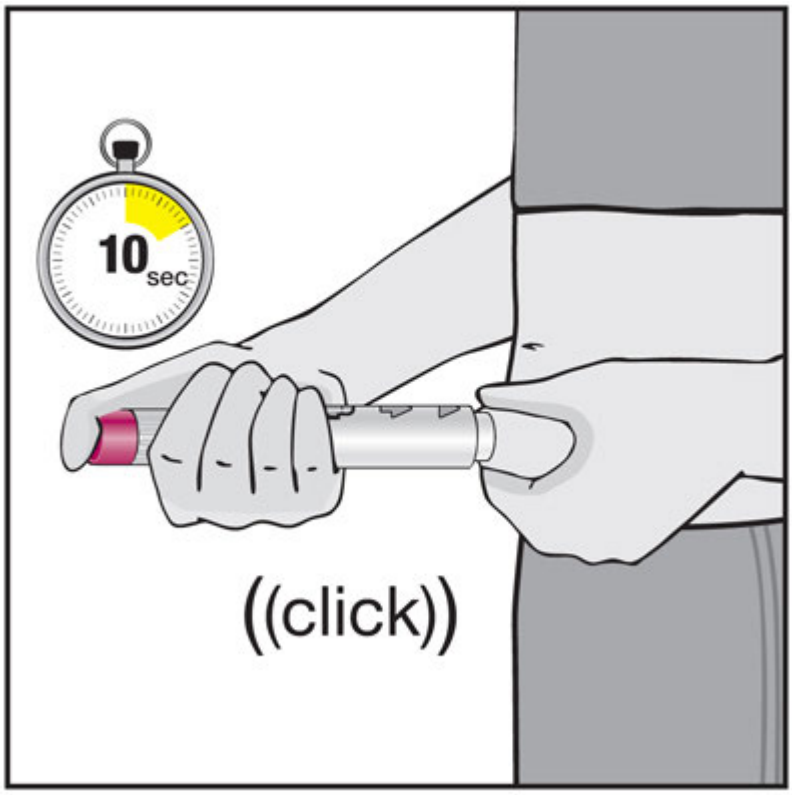
Figure J



18. Inject HUMIRA

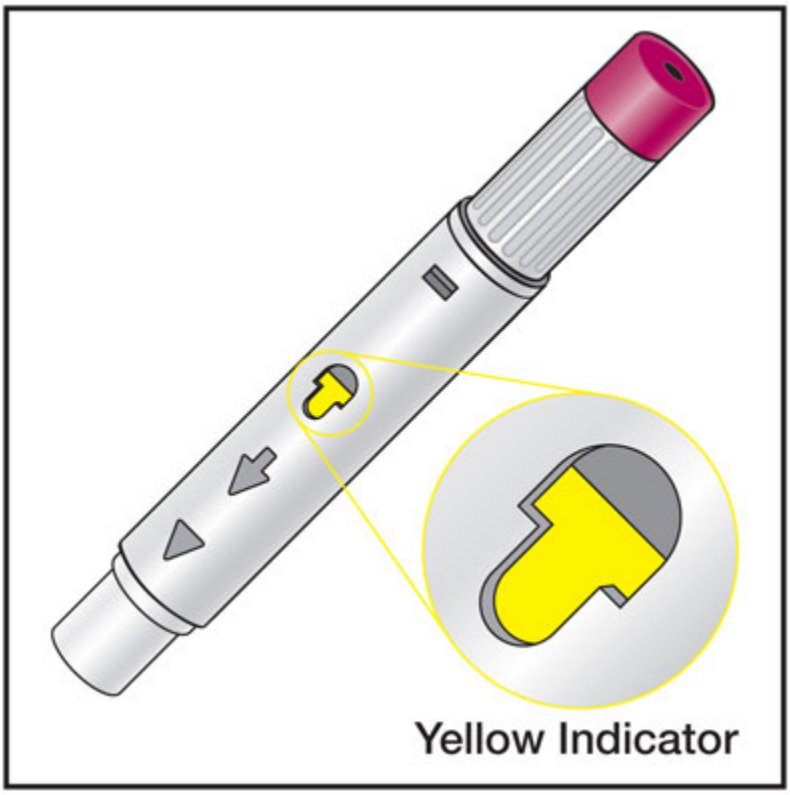
- With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

Figure K



- You will hear a loud ‘click’ when you press the plum-colored activator button. The loud click means the start of the injection.
- Keep pressing the plum-colored activator button and continue to hold the Pen against your squeezed, raised skin until all of the medicine is injected. This can take up to 10 seconds, so count slowly to ten. Keep holding the Pen against the squeezed, raised skin of your injection site for the whole time so you get the full dose of medicine.
- You will know that the injection has finished when the yellow marker fully appears in the window view and stops moving. See Figure L.

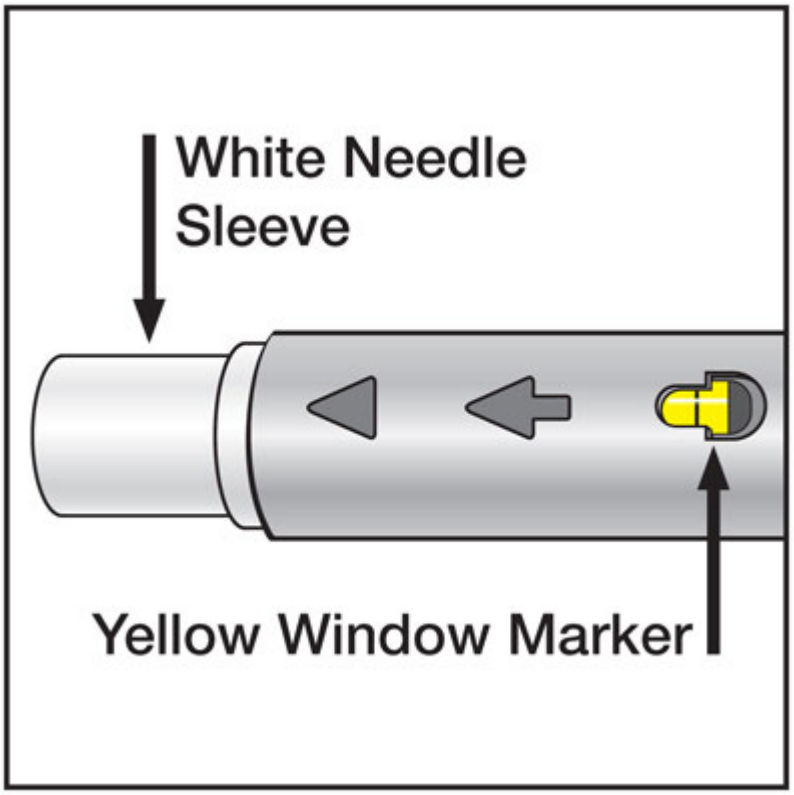
Figure L



19. When the injection is finished, slowly pull the Pen from your skin. The white needle sleeve will move to cover the needle tip. See Figure M.

- Do not touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure M



- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

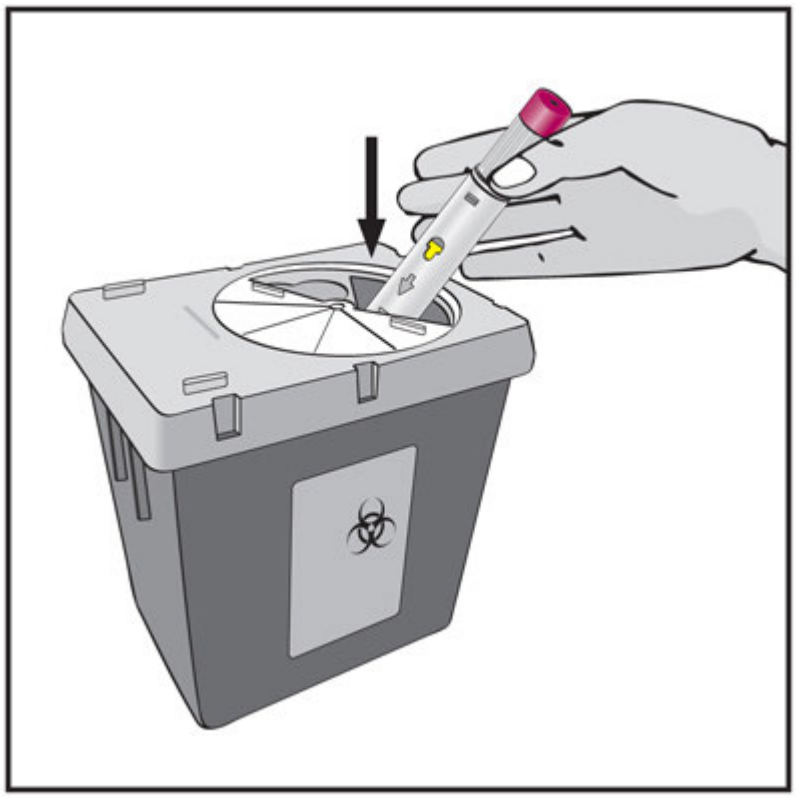
20. Dispose of your used HUMIRA Pen. See the section **"How should I dispose of the used HUMIRA Pen?"**

21. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of the used HUMIRA Pen?

- Put your Pen in a FDA-cleared sharps disposal container right away after use. See Figure N. **Do not throw away (dispose of) the Pen in your household trash.**
- Do not try to touch the needle. The white needle sleeve is there to prevent you from touching the needle.

Figure N



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, never re-use your HUMIRA Pens.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Content revised 09/2012

INSTRUCTIONS FOR USE

HUMIRA® (Hu-MARE-ah)

(adalimumab)

SINGLE-USE PREFILLED SYRINGE

Do not try to inject HUMIRA yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of HUMIRA at home, you should receive training on the right way to prepare and inject HUMIRA. It is important that you read, understand, and follow these instructions so that you inject HUMIRA the right way. Call your healthcare provider if you or your caregiver has any questions about the right way to inject HUMIRA.

How should I store HUMIRA?

- Store HUMIRA in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated HUMIRA may be used until the expiration date printed on the HUMIRA carton, dose tray and prefilled syringe.
- Do not use a prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush HUMIRA. The prefilled syringe is glass.
- **Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.**

Gather the Supplies for Your Injection

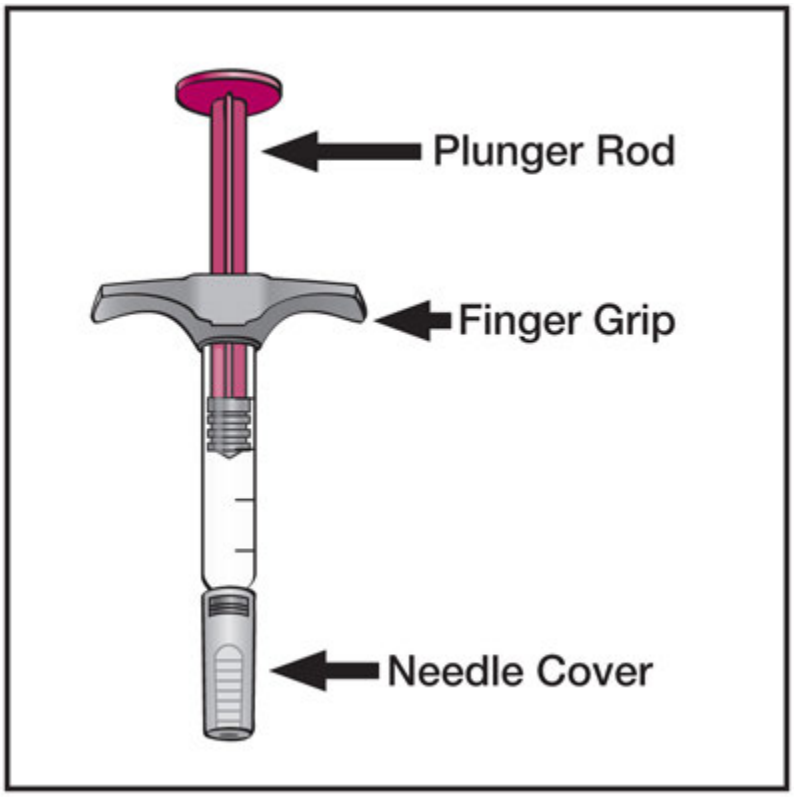
- You will need the following supplies for your injection of HUMIRA.
  Find a clean, flat surface to place the supplies on.
    - 1 alcohol swab
    - 1 cotton ball or gauze pad (not included in your HUMIRA carton)

- 1 HUMIRA prefilled syringe (See Figure A)
- 1 FDA-cleared sharps disposal container for HUMIRA prefilled syringe disposal (not included in your HUMIRA carton)

If you do not have all of the supplies you need to give yourself an injection, go to a pharmacy or call your pharmacist.

The diagram below shows what a prefilled syringe looks like. See Figure A.

Figure A



Check the carton, dose tray, and prefilled syringe

1. Make sure the name HUMIRA appears on the dose tray and prefilled syringe label.

2. **Do not use** and call your doctor or pharmacist if:

- the seals on top and bottom of the carton are broken or missing.
- the HUMIRA labeling has an expired date. Check the expiration date on your HUMIRA carton and do not use if the date has passed.
- the prefilled syringe that has been frozen or left in direct sunlight. See the section: **"How should I store HUMIRA?"** at the beginning of these Instructions for Use.

- the liquid in the prefilled syringe is cloudy, discolored or has flakes or particles in it. Make sure the liquid is clear and colorless.

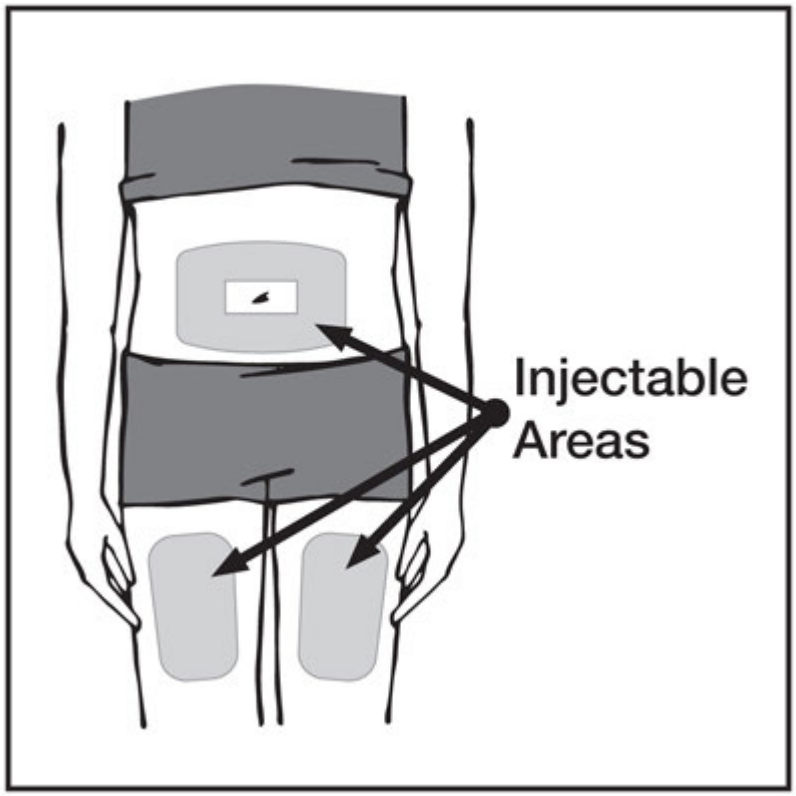
Choose the Injection Site

3. Wash and dry your hands well.

4. Choose an injection site on:

- the front of your thighs or
- your lower abdomen (belly). If you choose your abdomen, do not use the area 2 inches around your belly button (navel). See Figure B.

Figure B



- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before.
- **Do not** inject into skin that is:
    - sore (tender)
    - bruised
    - red
    - hard

- scarred or where you have stretch marks

- If you have psoriasis, do not inject directly into any raised, thick, red or scaly skin patches or lesions on your skin.
- Do not inject through your clothes.

Prepare the Injection Site

5. Wipe the injection site with an alcohol prep (swab) using a circular motion.

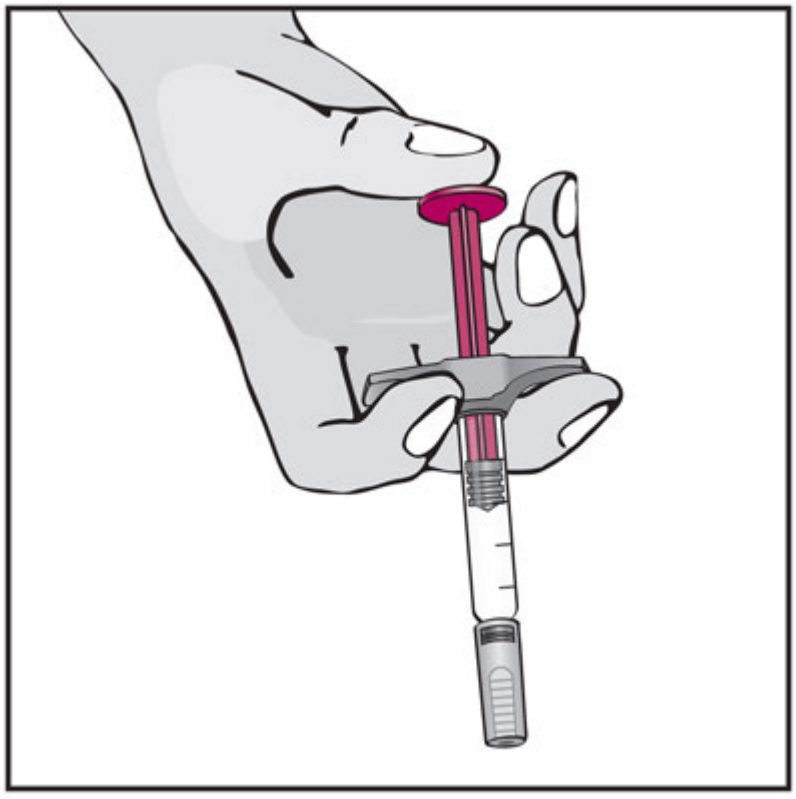
6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Check the fluid level in the syringe:

- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

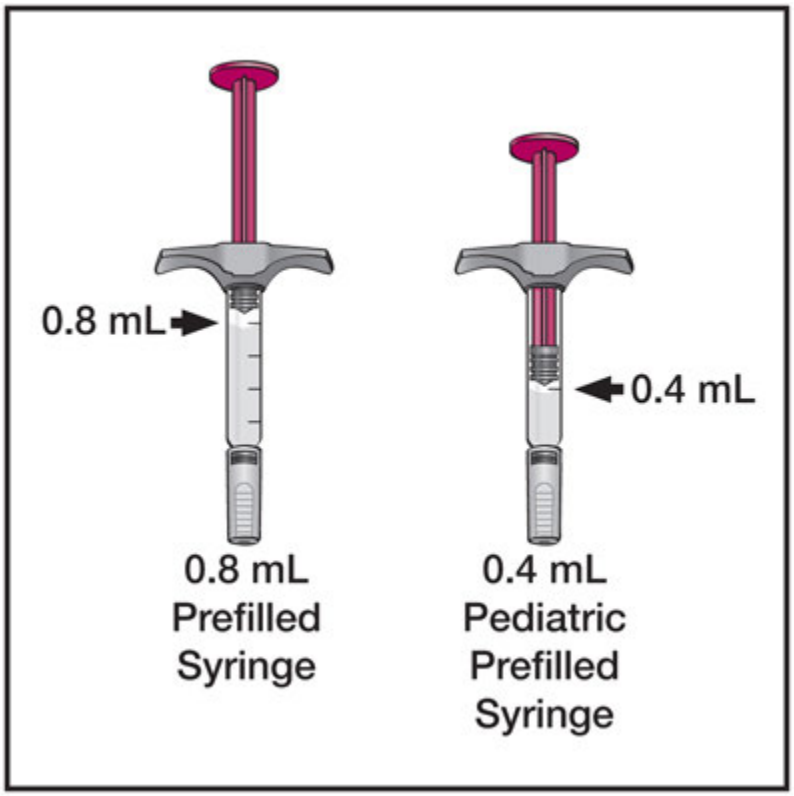
Figure C



- Hold the syringe at eye level. Look closely to make sure that the amount of liquid in the syringe is the same or close to the:
    - 0.8 mL line for the 40 mg prefilled syringe

- 0.4 mL line for the 20 mg pediatric prefilled syringe. See Figure D.

Figure D

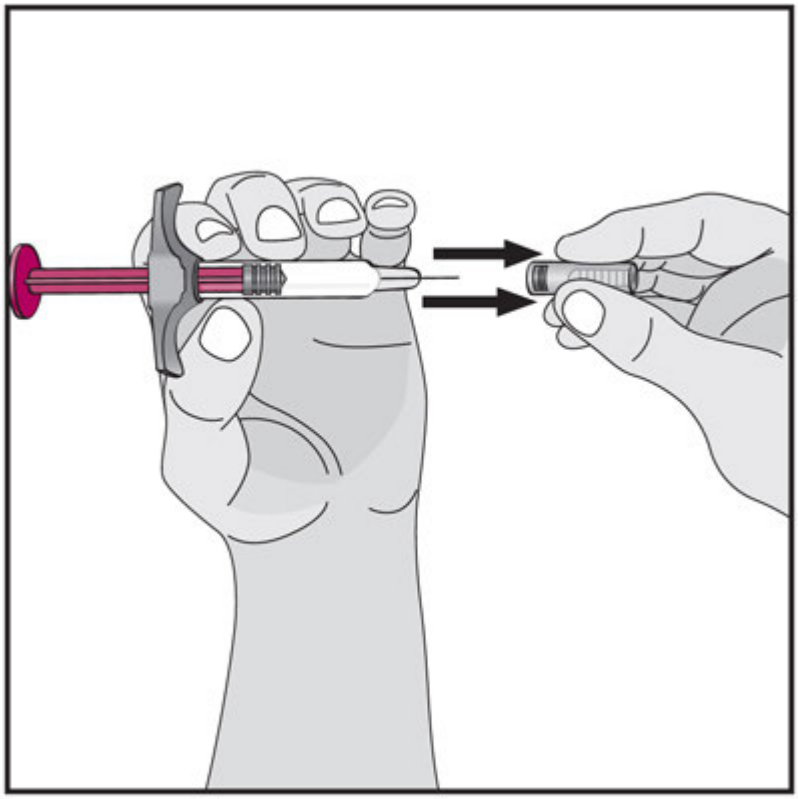


8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

9. Remove the needle cover:

- Hold the syringe in one hand. With the other hand gently remove the needle cover. See Figure E.
- Throw away the needle cover.

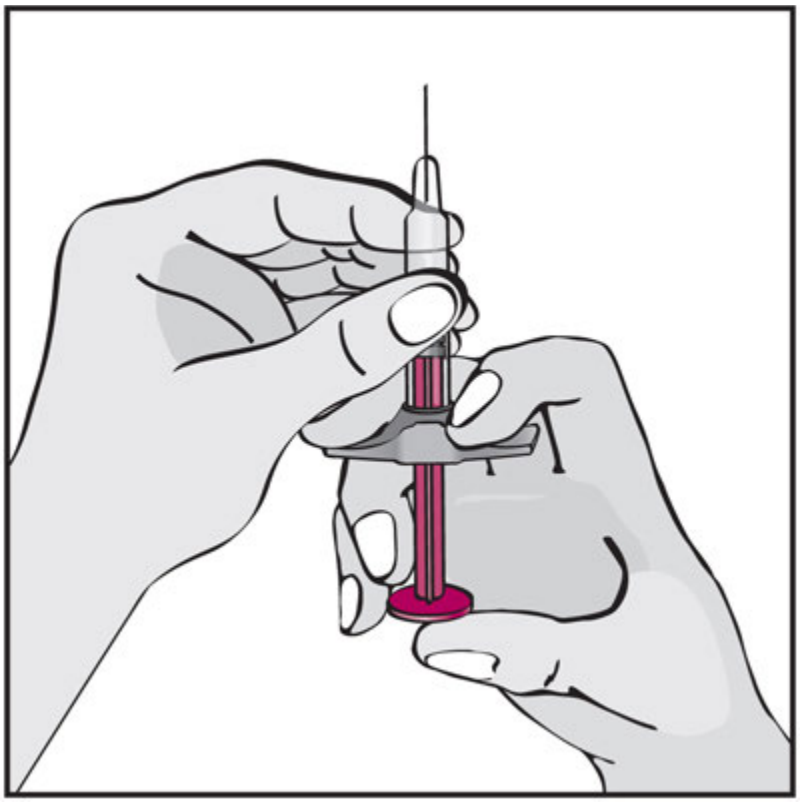
Figure E



- Do not touch the needle with your fingers or let the needle touch anything.

10. Turn the syringe so the needle is facing up and hold the syringe at eye level with one hand so you can see the air in the syringe. Using your other hand, slowly push the plunger in to push the air out through the needle. See Figure F.

Figure F



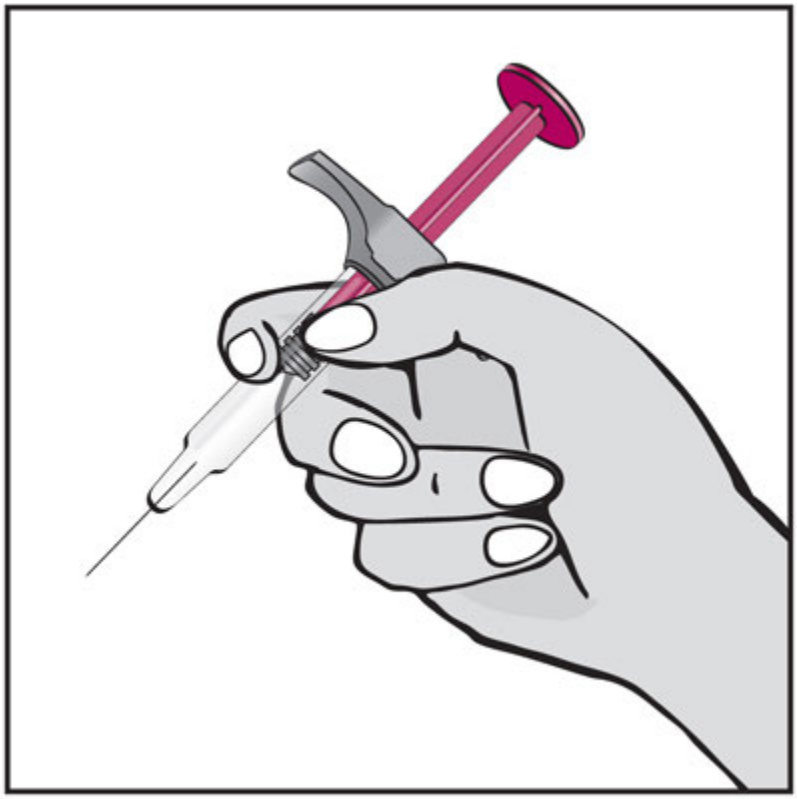
- You may see a drop of liquid at the end of the needle. This is normal.

Position the Prefilled Syringe and Inject HUMIRA

Position the Syringe

11. Hold the body of the prefilled syringe in one hand between the thumb and index finger. Hold the syringe in your hand like a pencil. See Figure G.

Figure G



- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure H.

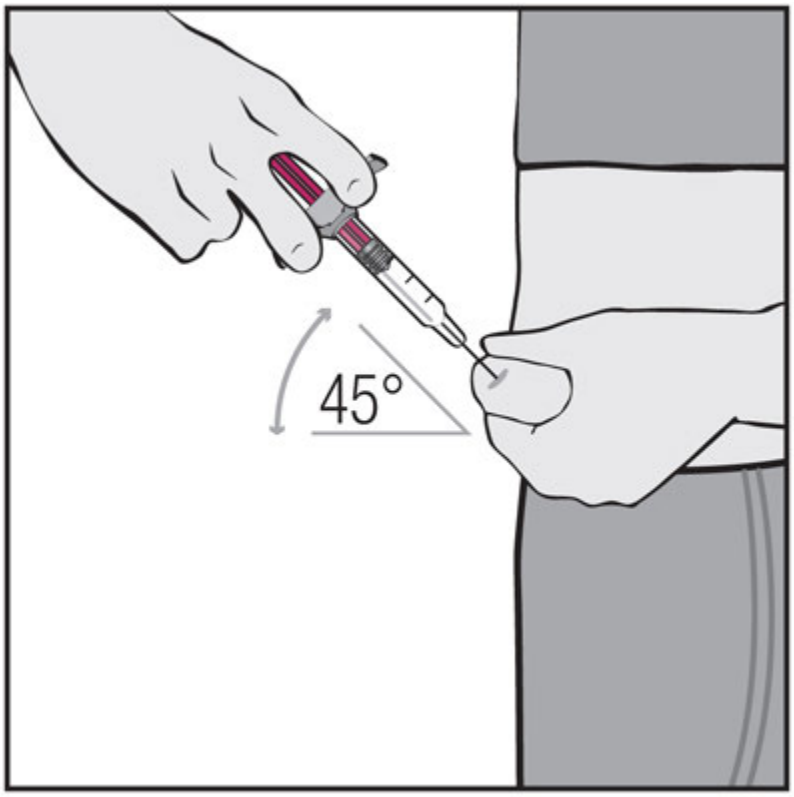
Figure H



Inject HUMIRA

12. Using a quick, dart-like motion, insert the needle into the squeezed skin at about a **45-degree angle**. See Figure I.

Figure I

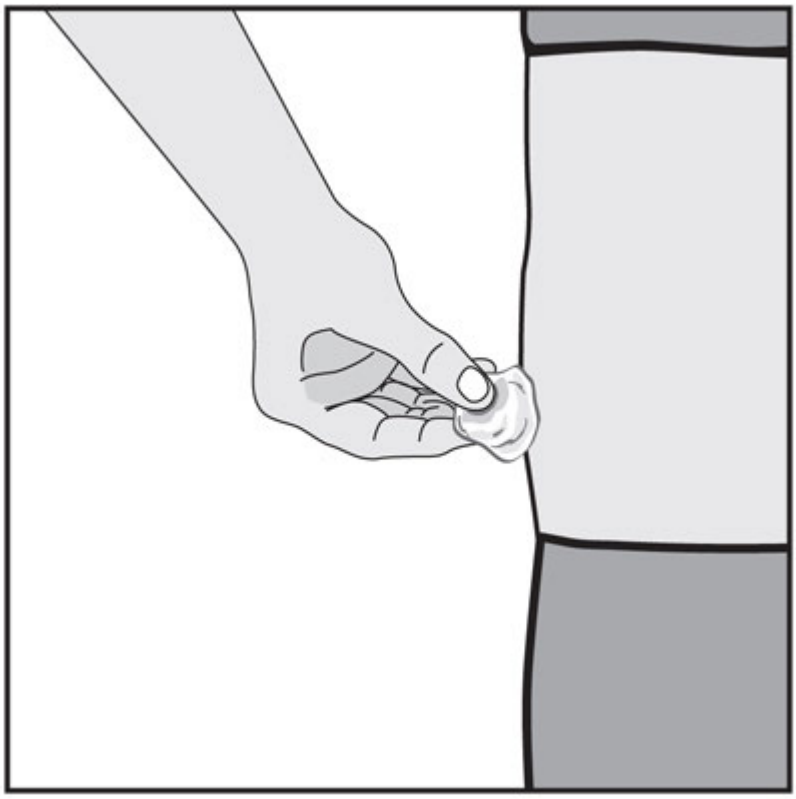


- After the needle is in, let go of the skin. Pull back gently on the plunger.

If blood appears in the syringe:

- It means that you have entered a blood vessel.
- **Do not inject HUMIRA.**
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. See Figure J.

Figure J



- **Do not** use the same syringe and needle again. Throw away the needle and syringe in your special sharps container.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- Repeat Steps 1 through 12 with a new prefilled syringe.

If no blood appears in the syringe:

- Slowly push the plunger all the way in until all of the liquid is injected and the syringe is empty.
- Pull the needle out of the skin while keeping the syringe at the same angle.
- Press a cotton ball or gauze pad over the injection site and hold it for 10 seconds. Do **not** rub the injection site. You may have slight bleeding. This is normal.

13. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

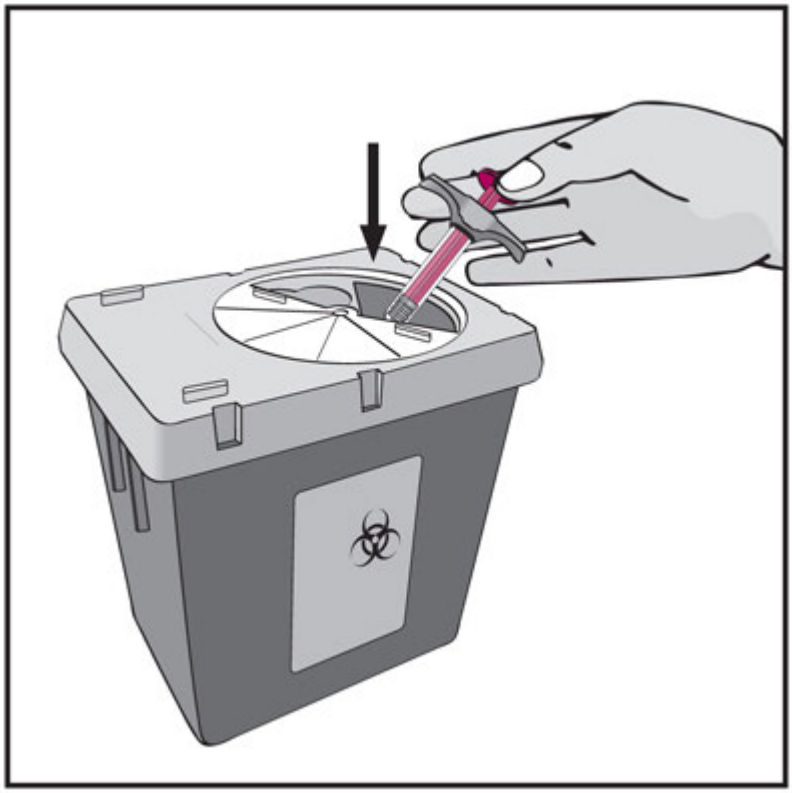
14. Keep a record of the dates and location of your injection sites. To help you remember when to take HUMIRA, you can mark your calendar ahead of time.

How should I dispose of used prefilled syringes and needles?

- **Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use.** See Figure K. **Do not throw away (dispose of) loose needles and syringes in your household trash.**

- Do not try to touch the needle.

Figure K



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- For the safety and health of you and others, needles and used syringes **must never** be re-used.
- The used alcohol pads, cotton balls, dose trays and packaging may be placed in your household trash.
- **Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.**
- **Always keep the sharps container out of the reach of children.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Content revised 09/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 28, 2012
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	125057/232 (sBLA)
Applicant Name	ABBOTT LABORATORIES
Date of Submission	March 30, 2012
PDUFA Goal Date	Original: November 25, 2011; Post-CR Revised September 28, 2012
Proprietary Name / Established (USAN) Name	Humira® / adalimumab
Dosage Forms / Strength	40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) 2. 40 mg/0.8 mL in a single-dose prefilled glass syringe 3. 20 mg/0.4 mL in a single-dose prefilled glass syringe
Proposed Indication(s)	Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP).
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Milton Fan, PhD Michael Welch, PhD
Medical Officer Review	Aisha Johnson, MD
DMA/OBP	Jun Park, Ph.D., Product Reviewer Ruth Cordoba-Rodriguez, Ph.D
Pharmacometrics	Nitin Mehrotra, Ph.D. Christine Garnett, Pharm. D.
Regulatory Program Management	Kevin Bugin
Clinical Pharmacology	Lin Zhou, Ph.D. Yow-Ming Wang Ph.D.
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.

Reference ID: 3196782

CDTL Review	Anil Rajpal, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Reference ID: 3196782

Signatory Authority Review Template

1. Introduction

This resubmission, received March 30, 2012, is a complete response to the CR letter, and represents the second review cycle for this sBLA. The Sponsor proposes to market adalimumab (Humira) for the following indication in adults:

1) reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. In this supplemental Biological License Application (sBLA), the Sponsor pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy. Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses of ulcerative colitis and inflammatory bowel disease.

The Applicant presents data from three phase 3 studies were included in this submission: M06-826 (the pivotal induction study), M06-827 (the pivotal maintenance study), and M10-223 (long-term single-arm, open-label trial that enrolled 498 patients). The endpoints for the two submitted pivotal trials are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.

Study M06-826 has an 8- or 12-week randomized, double-blind, placebo-controlled period which is followed by open-label treatment through Week 52. The objective was to evaluated adalimumab for the effectiveness of induction treatment. The study enrolled 576 subjects. The primary endpoint was clinical remission per Mayo score which is defined as total Mayo score ≤ 2 and no individual subscore > 1. (Mayo Score is a composite sore of UC disease activity ranging from 0 to 12 based on the sum of 4 sub scores. The higher the score is, the more severe the disease is. The four sub-scores include endoscopy, stool frequency, rectal bleeding and physician's global assessment.) Week 8 remission rate was 9.2% in the placebo arm and 18.5% in the adalimumab 160/80/40 arm (P=0.031). The adalimumab low dose arm (80/40/40) had a 10.0% clinical remission rate at week 8 which was not significantly different from placebo (P=0.833).

Study M06-827 is a 52-week randomized, double blind, placebo- controlled, multicenter study that evaluated adalimumab for the effectiveness of induction and maintenance treatment. The

Reference ID: 3196782

study enrolled 518 subjects. The ranked co-primary efficacy endpoints were the proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52. Week 8 remission rate was achieved by 9.3% of subjects in the placebo arm and 16.5% of subjects in the adalimumab 160/80/40 arm (P=0.019). Week 52 remission was achieved in 8.5% of subjects in the placebo arm and 17.3% of subjects in the adalimumab 160/80/40 arm (P=0.004).

Study M10-223 evaluated the long-term maintenance of response, safety and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827.

The concerns with this application initially involved the marginal efficacy noted in Study M06-826 and 827. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover, the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject. This issue was intimately related to the clinical meaningfulness of the data. I was concerned that the clinical development program lacks adequate justification of the balance of risk and benefit of adalimumab treatment for the induction and maintenance of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Given the known serious risks associated with the use of Humira, the data presented in the current Application do not adequately demonstrate that Humira has clinically meaningful efficacy. Further, the results of the submitted studies show that the benefit of Humira for reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy does not outweigh the risks. Given the small treatment effect and E-R analysis results suggest that higher dose may achieve greater treatment effect [for induction], the sponsor should explore higher doses for inducing remission in a clinical trial that define an appropriately labeled dose related to clinical efficacy of Humira. Without an appropriately defined dose, the benefit-risk assessment for Humira may not be favorable, a conclusion that is supported by the fragility of the data. This conclusion is demonstrated through sensitivity analyses revealing that Study M06-826 could be a "negative" study, if a change in the responder status of 1 subjects in the adalimumab 160/80/40 group from responder to non-responder, or in the responder status of just 1 placebo subject from non-responder to responder. This impacts the interpretation of the benefit risk assessment relative to the differences in improvement in clinical remission rates reported (treatment difference in clinical remission at Week 8 of 9.3% and 7.2% in Studies 826 and 827, respectively and treatment difference in sustained clinical remission at Weeks 8 and 52 of 4.4% in Study 827), in light of the known risks of Humira (such as malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome).

Reference ID: 3196782

Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications.

In summary the data in the original application did not establish that adalimumab is effective and safe for the treatment of patients with moderately to severely active ulcerative colitis. I have concluded that there was not sufficient evidence of clinical benefit, which coupled with some concerns of safety, makes it impossible for me to justify the marketing of this product without additional key information. The decision to provide a complete response was supplemented by convening an advisory committee in August 2012 to address a path forward.

Subsequent to the execution of a Gastroenterology Drug Advisory Committee held on August 28, 2012 to discuss this application, the nearly unanimous recommendation by the experts was approval of this application. Discussion of the clinical meaningfulness of the data as compared to statistical significance of the primary endpoint analysis was featured topics during the GIDAC. The majority of Committee members believed that the observed treatment differences, small in magnitude but statistically significant, do represent a clinically meaningful benefit to the population of UC patients, primarily because of the continuing need for treatment alternatives. The majority further believed that the demonstrated benefit is sufficient to outweigh the risks and that the benefit-risk decision can be made by individual patients with their providers.

Given the adequacy of clinical trials to sufficiently demonstrate efficacy and the Committee's recommendations that these results are meaningful and outweigh the product's risks, I have agreed with the team recommendation of approval of Humira for this indication. In fact the Team Leader Dr. Welch of Statistics has stated: "The sponsor's complete response satisfactorily addressed the statistical issues in the CR letter. Although much of the resubmission was based on exploratory analyses, the results should be considered supportive. From a statistical perspective, both studies 826 and 827 met their primary objective to show induction of clinical remission at week 8. However, replication of effect was only seen in patients who did not have prior UC therapy. Study 827 demonstrated a treatment effect for induction at 52 weeks and a small effect for induction at both 8 and 52 weeks. The study was not designed to support maintenance of remission, since subjects were not re-randomized at week 8; however, the given results would seem to support a "sustained remission" claim under the condition that completers were in remission during the time-course of study, and that patients who terminated early were not in remission at time of withdrawal.

In light of the secondary reviews, however, we recommend that the product be indicated for "inducing and sustaining remission", which is more specific than "achieving" remission but does not include the more stringent efficacy claim of "maintenance of remission". Given our uncertainty about the long-term benefit of Humira to sustain remission, we recommend the drug be continued beyond 8 weeks only in patients who have achieved remission within that time. Further, we recommend that the product be indicated only for TNFα-antagonist naïve patients, because the evidence failed to demonstrate benefit in patients with prior exposure to these products.

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In addition, there will be a number of postmarket commitments (PMCs) from the Sponsor as more fully detailed in this review consistent with the GIDAC recommendations described below. These include studies related to exploring risk of HSCTL, long-term safety of serious infections and malignancies and long-term effectiveness in a comparative registry, evaluating low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events, conducting an assessment of anti-adalimumab antibody response to Humira, with a validated assay capable of sensitively detecting anti-adalimumab antibodies, conducting a trial to evaluate efficacy and safety of induction regimens at doses higher than 160/80 mg and evaluating the safety, efficacy, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. The specific indication approved will be modified from the Applicant's initial proposal and specifically state: Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers

2. Background

The reader is referred to Dr. Peterson's Clinical Review for further discussion of the regulatory history concerning Humira. Briefly, HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. In this supplemental Biological License Application (sBLA), the applicant pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

3. CMC

The reader is referred to the CMC Review by Jun Park. The CMC Reviewer noted that the Clinical Pharmacology Reviewer raised a concern about the sensitivity of both AAA assays to product interference (i.e., neither the original nor the new AAA assay is able to appropriately measure AAA because of product interference) (see Section 5.1 of this CDTL Review). The CMC Reviewer concluded that an assay with improved drug tolerance should be developed. The following deficiency is included in the CRL:

> "The immunogenicity assay was not adequate. Develop, qualify and implement an improved validated anti-adalimumab antibody (AAA) assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the

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time of patient sampling. Until assays have been developed and validated, patients samples collected from clinical studies should be banked under appropriate storage conditions."

There were no new CMC data in the resubmission, and no additional review of CMC data was performed in the current review cycle.

4. Nonclinical Pharmacology/Toxicology

No new review issues are identified and no nonclinical issues were raised.

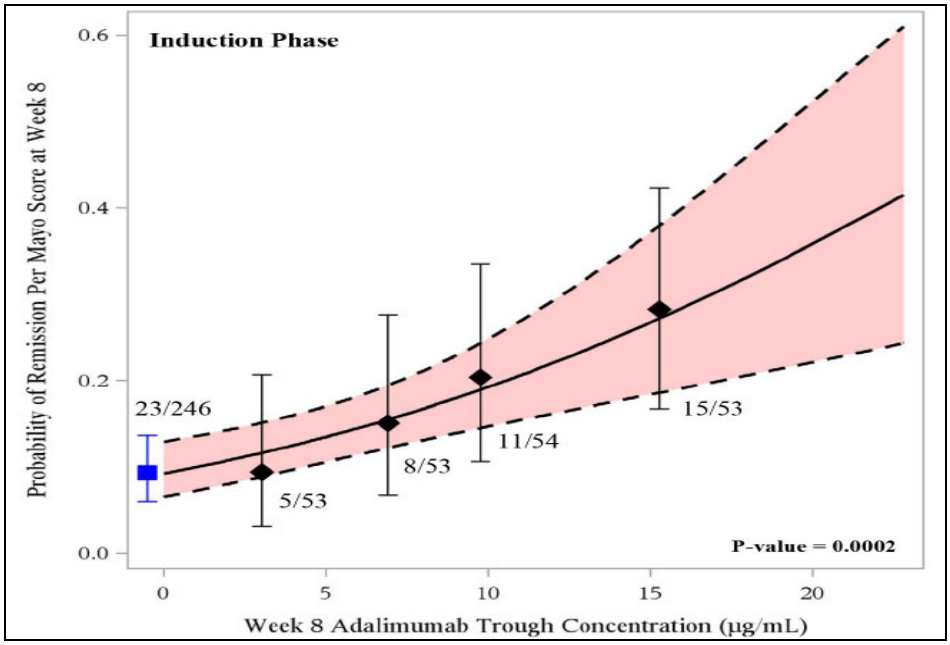
5. Clinical Pharmacology/Biopharmaceutics

I share my agreement regarding concerns of Dr. Zhou's initial review that there are significant concerns regarding the lack of complete understanding of the exposure response relationship of adalimumab in inducing and maintaining remission in patients with moderately active to severe ulcerative colitis. The exposure-response analysis conducted based on data from Study M06-827 suggested a higher induction dose might achieve a greater treatment effect for the induction of clinical remission at Week 8. The Clinical Pharmacology Reviewer stated that this conclusion is mainly based on two observations as summarized by Dr. Rajpal:

1) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression. The figure below demonstrates the exposure-response relationship for clinical remission at Week 8 suggesting that higher exposures may be associated with a higher clinical remission rate. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Multivariate logistic regression was performed to determine if the relationship between Week 8 adalimumab trough concentration and Week 8 clinical remission was confounded by baseline Mayo score and prior anti-TNF exposure. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant (p=0.0003).

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Figure 1. Logistic Regression Model of the Probability of Remission per Mayo score at Week 8 as a function of Week 8 Adalimumab Trough Concentrations.

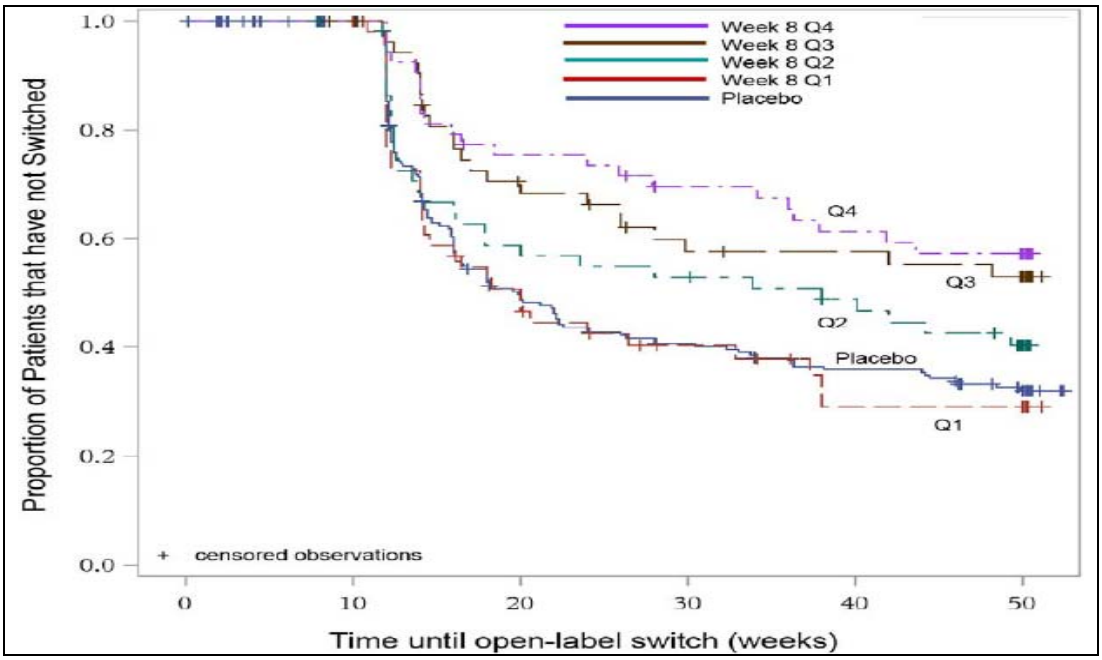


The figure above is taken from Page 17 of the Clinical Pharmacology Review by Lin Zhou.

As a follow up concern, patients with lower exposures in the induction phase were unable to maintain response and switched to open-label treatment earlier than patients with higher exposures. The figure below demonstrates that subjects who had lower Week 8 adalimumab trough concentrations lost response earlier than the subjects with higher Week 8 concentrations. This provides additional evidence that exposures achieved by the 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that Week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy at baseline and baseline Mayo score.

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Figure 2. Kaplan-Meier Plot of the Proportion of Subjects who have Not Switched vs. Week 8 Adalimumab Trough Concentration Quartile*



***Censored observations are indicated by the "+" symbol.**

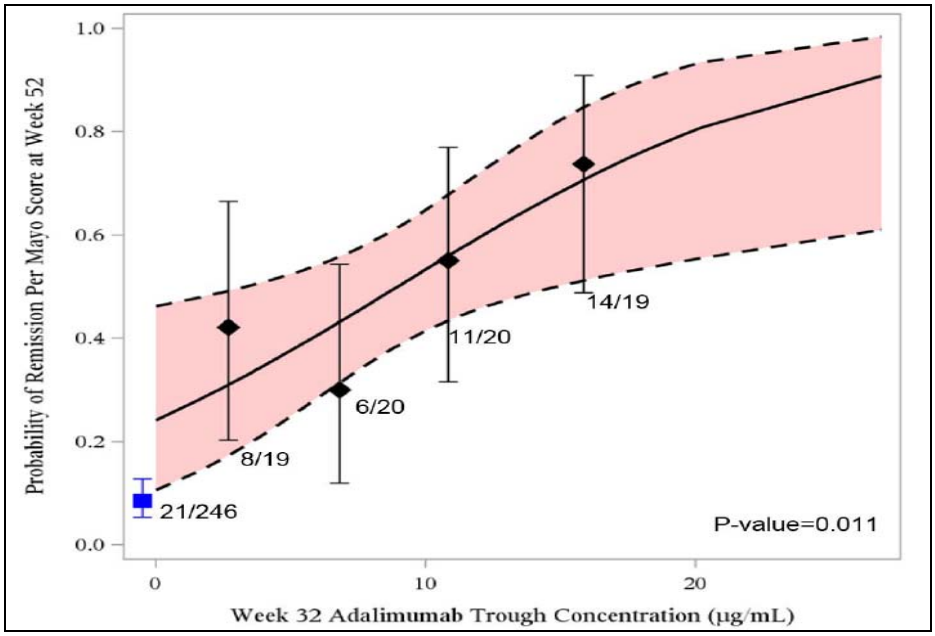
The figure above is taken from Page 18 of the Clinical Pharmacology Review by Lin Zhou.

Maintenance Phase:

The Clinical Pharmacology Reviewer concluded that a robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Although the model relating steady state adalimumab trough concentrations to Week 52 remission demonstrates a weak trend in exposure-response (p=0.01, see figure below), suggesting a higher dose may provide additional benefit, the analysis is based on only 78 patients (31% of the total treatment population) who remained in the double-blind phase throughout the trial and had PK data. Other limitations noted by the Clinical Pharmacology Reviewer included the following: (a) The analysis dataset included non-remitters at Week 8. (b) Only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline Mayo score and prior anti-TNF use. (c) The data used in this analysis may not be representative of the actual treatment population since the clinical remission rate is 33% (43/132) for patients who remained in the double-blind treatment phase compared to 50% (39/78) for subjects who remained in double blind phase and had PK data.

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Figure 3. Logistic Regression Model of the Probability of Remission per Mayo Score at Week 52 as a Function of Week 32 Adalimumab Trough Concentrations.



The figure above is taken from Page 19 of the Clinical Pharmacology Review by Lin Zhou.

In addition there is lack of understanding the impact of Immunogenicity on Adalimumab Pharmacokinetics. No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only very small number of subjects had confirmed antibody status. The assessment of immunogenicity incidence was not adequate in the current submission. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration (≥2 mcg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients. Dr. Zhou states: "Our exposure-response analysis indicates that the dosing has not been fully explored. Without a better defined dosing paradigm the clinical efficacy of Humira in this population can not be considered adequately defined. No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because majority of the subjects in the phase 3 studies were not tested for anti-adalimumab antibodies due to drug interference. In order to obtain an adequate adalimumab immunogenicity profile, we recommend that the Sponsor (1) develop an assay with improved drug tolerance to allow detecting anti-adalimumab antibodies in the presence of adalimumab drug concentration in the study samples collected from patients during treatment, and/or 2) collect post-dose samples at time points where the adalimumab drug concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL)." From a Clinical Pharmacology perspective, the combination of a lack of adequate dose-response combined with a lack of adequate immunogenicity information will limit our ability to write adequate labeling concerning the use of this product.

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Based on the feedback of the GIDAC concerning these issues, there was no change in the perspectives of the Clinical Pharmacology reviewers. The confidence in the dataset suggesting that the exposure-response analysis suggested that a higher induction dose would lead to a higher treatment effect in induction of clinical remission, the Clinical Pharmacology Reviewers recommended studies to study a higher induction dose. Communication of the PMCs will be discussed below in the approval letter and more fully detailed in section 13 of this review.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Humira is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

In the original cycle of this application, the reader is referred to Dr. Rajpal's CDTL memorandum for further review and complete information of historical efficacy and safety data related to clinical trial and exposure data related to adalimumab. Dr. Rajpal recommends a Complete Response to this application for the reasons stating: "Your submission does not provide substantial evidence to establish the efficacy of Humira for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. To address this deficiency, we recommend that you provide additional evidence of efficacy from either: (a) comprehensive re-analyses of outcome data from the clinical trials you have already conducted with Humira; or (b) additional adequate and well-controlled trial(s)." It is my decision that the Agency plans to discuss the efficacy data presented in this application at a future meeting of the Gastrointestinal Drugs Advisory Committee

I do not agree that conduct of comprehensive re-analyses of outcome data would adequately address the deficiency. Given the known serious risks associated with the use of Humira, the data presented in the current application do not adequately demonstrate that Humira has clinically meaningful efficacy. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject. This impacts the interpretation of the benefit risk assessment relative to the differences in improvement in clinical remission rates reported (treatment difference in clinical remission at Week 8 of 9.3% and 7.2% in Studies 826 and 827, respectively and treatment difference in sustained clinical remission at Weeks 8 and 52 of 4.4% in Study 827) and the known risks of Humira (such as malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome).

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The data in the original application did not allow the establishment of a favorable benefit risk assessment for adalimumab for the treatment of patients in reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. Despite the contrast to already approved medications for the same indication, it is important to understand that there are limitations associated with the use of cross study comparisons. The data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indication. The marginal differences in efficacy observed with adalimumab and the fragility of the data as determined by sensitivity analyses leads to conclude that this application should receive a Complete Response.

It is my conclusion to defer to the counsel of the 2012 Advisory Committee that discussed this application; we have made a revised Risk Benefit assessment approving adalimumab for the indication (see below). The Advisory Committee was asked to comment on the clinical significance of the marginal differences exhibited in efficacy differences between adalimumab and placebo and the corresponding determination of benefit and risk with this application.

In the Complete response submission by the Applicant, numerous exploratory analyses were conducted as outlined by Drs. Gottlieb and Fan in their reviews. Specifically these included primary and secondary analyses of Study 826 using the ITT-E population (i.e., all patients enrolled that received study drug or placebo);

- integrated primary and secondary analyses across Studies 826 and 827;
- additional exploratory analyses from Study 827 (e.g., clinical response based on partial Mayo score at Weeks 2, 4, and 8 and clinical response based on full Mayo score at Week 8);
- re-analysis of full and partial Mayo scores at Baseline and Week 52 using average of last 3 days (rather than standard "worst-ranked" methodology)-Study 827;
- all-cause and UC-related hospitalizations (pooled across Studies 826 and 827); and
- exploratory analyses of clinical remission and clinical response status at Week 52 in the subgroup of patients from Study 827 in clinical response at Week 8.

The following analyses were conducted by the sponsor in an attempt to combine safety and efficacy data and will be reviewed in section 7.

- serious adverse event (SAE)-adjusted days in remission
- number of patients who discontinued due to adverse events (AEs) relative to number of patients in remission at Weeks 8 and 52
- Net Efficacy Adjusted Risk (NEAR) analysis
- Number Needed to Harm (NNH) analyses

Initially my impression and that of the reviewers that the numerous post-hoc analyses are insufficient to support approval and statistical evaluation with p values pose no strong support for the approval decision. From the GIDAC, it was clear that the data were interpreted by the AC experts as contributing clinical meaningfulness to the submitted data. For example, the

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minutes captured the following assessments by the GI experts: *Those voting "Yes" commented about unmet need, compliance & convenience issues, which favored having adalimumab as a treatment option. The study did show statistical significance as compared to placebo, at week 8, albeit the differences being marginal. One member noted the long record of use of this drug and of the class of drugs. Several noted that currently given few treatment choices adalimumab would be another option, especially for difficult to treat patients. Committee members hence endorsed Humira voting that it resulted in clinically meaningful benefit. Even the marginal benefit was acceptable given the high disease burden with regards to its impact on quality of life."* It should be stated though that the analyses offered by the Statistical review still were not completely satisfied with the conclusions of the GIDAC relative to the clinical meaningfulness of the dataset. As noted by Dr. Rajpal, "The statistical reviewer continues to be concerned about the high amount of missing data and commented that with approximately 70% missing data, the results for sustained clinical remission may not be reliable. This reviewer notes that this is not an approvability issue." The Statistical Team Leader also stated, "The sponsor's complete response satisfactorily addressed many of the statistical issues raised in the CR letter. Although much of the resubmission was based on exploratory analyses, the results should be considered supportive." From a statistical perspective, both studies 826 and 827 met their primary objective to show induction of clinical remission at week 8. However, replication of effect was only seen in patients who did not have prior UC therapy using TNF blockers. Study 827 demonstrated a treatment effect for induction at 52 weeks and a small effect for induction at both 8 and 52 weeks. The GIDAC supported the clinical meaningfulness but the population will be refined to reflect the strength of the data.

I will agree with the Clinical and Statistical recommendation for approval of Humira for the proposed indication with modifications above noted to the modified indication to stress the approvability of the data to support the use of Humira only in TNF blocker naïve treated patients.

8. Safety

The reader is referred to Dr. Peterson's Clinical review and summary by Dr. Rajpal for review of safety issue. There are known serious adverse events associated with the use of Humira. These known risks include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome.

The Clinical Reviewer concluded that there was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies.

The GIDAC concluded that there was not a significant safety issue with approval of Humira for this indication.

9. Advisory Committee Meeting

An Advisory Committee meeting was convened August 28, 2012 to address the path forward for this application. In my initial opinion rendered supporting the Complete Response action, I concurred with Clinical and statistical reviewers that the clinical development program did not

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support the benefit outweighing the risk of adalimumab treatment for the induction and maintenance of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy, an advisory committee is necessary to identify future path. Given the small treatment effect and E-R analysis results suggest that higher dose may achieve greater treatment effect [for induction], the sponsor should explore higher doses for inducing remission in a clinical trial. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications. Support for these initial review impressions is substantiated by the opinions of the GIDAC recommending that further dose exploration with higher doses be performed as a postmarketing requirement. Details of these postmarketing commitments are described below.

The data in the original BLA did not establish that adalimumab is effective and safe for the treatment of patients with moderately to severely active ulcerative colitis. I had concluded that there was not sufficient evidence of clinical benefit, which coupled with some concerns of safety, made it impossible for me to justify the marketing of this product without additional key information. Subsequent to the execution of a Gastroenterology Drug Advisory Committee held on August 28, 2012 to discuss this application, the nearly unanimous recommendation by the experts was approval of this application. Discussion of the clinical meaningfulness of the data as compared to statistical significance of the primary endpoint analysis was featured topics during the GIDAC. The majority of Committee members believed that the observed treatment differences, small in magnitude but statistically significant, do represent a clinically meaningful benefit to the population of UC patients, primarily because of the continuing need for treatment alternatives. The majority further believed that the demonstrated benefit is sufficient to outweigh the risks and that the benefit-risk decision can be made by individual patients with their providers.

Given the adequacy of clinical trials to sufficiently demonstrate efficacy and the Committee's recommendations that these results are meaningful and outweigh the product's risks, I have agreed with the team recommendation of approval of Humira for this indication. However, we recommend that the product be indicated for "inducing and sustaining remission", which is more specific than "achieving" remission but does not include the more stringent efficacy claim of "maintenance of remission". Given our uncertainty about the long-term benefit of Humira to sustain remission, we recommend the drug be continued beyond 8 weeks only in patients who have achieved remission within that time. Further, we recommend that the product be indicated only for TNFα-antagonist naïve patients, because the evidence failed to demonstrate benefit in patients with prior exposure to these products. As discussed below in Labeling Section 12, the notation of these specific limitations will be noted.

In addition, there will be postmarket commitments (PMCs) from the Sponsor more fully described in Section 13.2 Risk Benefit. The specific indication approved will be modified from the Applicant's initial proposal and specifically state: Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-

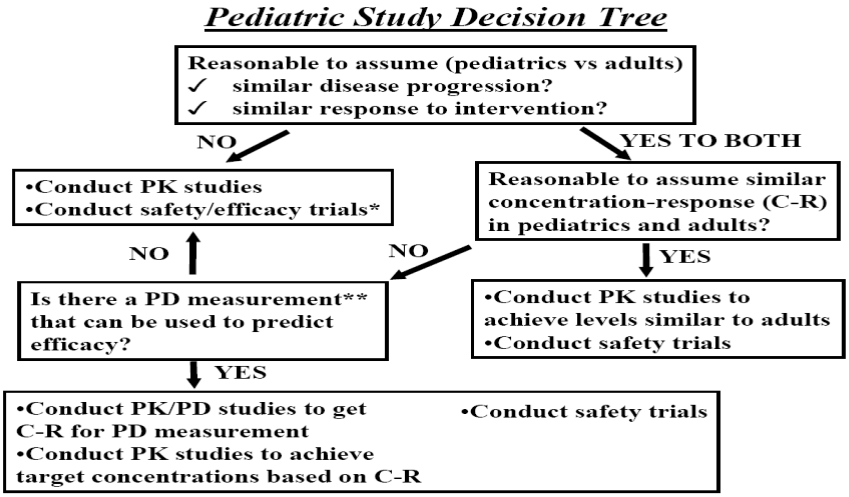
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mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

10. Pediatrics

The Pediatric clinical development program would need to validate appropriate endpoints for study in children with moderately to severe ulcerative colitis. The lack of complete understanding the identification of an effective dose of adalimumab in adults would preclude the adoption of extrapolation to children with moderately to severe UC as the basis for extrapolation is understanding the exposure response characteristics as discussed below. The role of pharmacokinetics in pediatric clinical trials is discussed in the FDA guidance **Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications[1].** The Pediatric Study Decision tree from the FDA exposure relationship guidance depicts the role of PK and PD in the development of pediatric clinical trials (see below, excerpted from guidance).

APPENDIX B: PEDIATRIC DECISION TREE INTEGRATION OF PK-PD



From the recent Advisory committee of Remicade in ulcerative colitis (*Gastrointestinal Drugs Advisory Committee (GIDAC)* Hilton Washington DC/Silver Spring, Silver Spring, Maryland **July 21, 2011 *Summary Minutes)***, it is was deemed to be reasonable to extrapolate efficacy from adults with properly conducted clinical trials based on the assumption that the course of ulcerative colitis and its response to treatment in adult and pediatric patients are sufficiently similar to be able to extrapolate efficacy from adult to pediatric patients. *The committee unanimously agreed that there was sufficient and well supported data to extrapolate from adult to pediatric patients for the induction of clinical remission.*

In this situation it should be noted that Humira has orphan designation, PREA does not apply to the adult indication as the pediatric indication has orphan status (designation date of May 11, 2011) as noted by Dr. Rajpal in his review. It is not clear whether the Applicant is still pursuing a development plan for pediatric UC given the orphan designation status but a

[1] http://www.fda.gov/cder/guidance/index htm

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postmarketing commitment will be submitted as part of the approval letter more fully delineated in Section 13.2 Risk Benefit below.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

Other issues include the lack of QT evaluation for adalimumab as discussed by Dr. Rajpal, but absence of preclinical concerns or post marketing experience precludes the need for further testing.

11.2 Office of Scientific Investigations (OSI) Audits

A site inspection was conducted by the Division of Scientific Investigations (DSI) of Site 29080 of Study 826 (Location: Vaughn, Ontario, Canada; Investigator: Susan Greenbloom, M.D.) This site was selected because it had the highest enrollment (approximately 10% of the patients in Study 826). No regulatory violations were observed during the inspection. DSI recommended that data from the inspected site can be used in support of the sBLA. For further details, the reader is referred to the CDTL memorandum.

12. Labeling

The most important changes to labeling include:

- Indications and Usage (Section 1.6 of Label): Rather than the wording proposed in the initial submission (inducing and maintaining clinical remission) or in the re-submission (achieving clinical remission), the wording of "inducing and sustaining clinical remission" was used. In addition, "inadequate response to conventional therapy" was replaced with "inadequate response to immunosuppressants such as corticosteroids, azathioprine, or 6-mercaptopurine (6-MP)" to describe the population that was studied. Further, the wording of "reducing signs and symptoms" was removed. Finally, the following statement was added: "The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers."

- Dosage and Administration (Section 1.4 of Label): The Applicant's proposed statement to only continue Humira in patients that have shown [redacted] (b) (4) was replaced with a statement to only continue Humira in patients that have shown evidence of "remission" by eight weeks. In addition, the Applicant's proposed statement [redacted] (b) (4) was removed.

- Clinical Studies (Section 14.6): [redacted] (b) (4) (b) (4) A paragraph describing the results in the subgroup of patients with prior TNFα-antagonist use was added.

Further details regarding other labeling changes are referred to the CDTL memorandum.

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13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:
All reviewers have recommended approval for which the Signatory agrees in the current resubmission cycle for this BLA.

13.2 Risk Benefit Assessment:
Given the known serious risks associated with the use of Humira, the data presented in the original Application did not adequately demonstrate that Humira has clinically meaningful efficacy. The data in the original application did not allow the establishment of a favorable benefit risk assessment for adalimumab for the treatment of patients in reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications.

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Given the adequacy of clinical trials to sufficiently demonstrate efficacy and the Committee's recommendations that these results are meaningful and outweigh the product's risks, I have agreed with the team recommendation of approval of Humira for this indication. However, we recommend that the product be indicated for "inducing and sustaining remission", which is more specific than "achieving" remission but does not include the more stringent efficacy claim of "maintenance of remission". Given our uncertainty about the long-term benefit of Humira to sustain remission, we recommend the drug be continued beyond 8 weeks only in patients who have achieved remission within that time. Further, we recommend that the product be indicated only for TNF blocker naïve patients, because the evidence failed to demonstrate benefit in patients with prior exposure to these products.

The specific indication approved will be modified from the Applicant's initial proposal and specifically state: Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP).

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

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There are no requirements for postmarketing risk evaluation.

Recommendation for other Postmarketing Requirements and Commitments

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #1 A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

The timetable you submitted on September 26, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	09/2019
Final Report Submission:	09/2020

PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Study Completion:	12/2027
Final Report Submission:	12/2029

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PMR #3 Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

PMR #4 Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2013
Study Completion: 03/2018
Final Report Submission: 03/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known risk of serious adverse events, including opportunistic infections and malignancies, in patients receiving higher doses of adalimumab.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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PMR #5 Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

PMR #6 A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC #7 Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed

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during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	06/2013
Trial Completion:	06/2018
Final Report Submission:	12/2019

Reference ID: 3196782

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW E MULBERG

09/28/2012

Division Deputy Director
DGIEP
Signatory Authority

Summary Review for Regulatory Action

Date	November 21, 2011
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	125057/232 (sBLA)
Applicant Name	ABBOTT LABORATORIES
Date of Submission	January 25, 2011
PDUFA Goal Date	November 25, 2011
Proprietary Name / Established (USAN) Name	Humira® / adalimumab
Dosage Forms / Strength	40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen) 2. 40 mg/0.8 mL in a single-dose prefilled glass syringe 3. 20 mg/0.4 mL in a single-dose prefilled glass syringe
Proposed Indication(s)	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy
Action/Recommended Action for NME:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Milton Fan, PhD Michael Welch, PhD
Medical Officer Review	Aisha Johnson, MD
DMA/OBP	Jun Park, Ph.D., Product Reviewer Ruth Cordoba-Rodriguez, Ph.D
Pharmacometrics	Nitin Mehrotra, Ph.D. Christine Garnett, Pharm. D.
Clinical Pharmacology	Lin Zhou, Ph.D. Yow-Ming Wang Ph.D.
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.
CDTL Review	Anil Rajpal, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Reference ID: 3200370

DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Reference ID: 3200370

Signatory Authority Review Template

1. Introduction

In this NDA supplement, the applicant proposes to market adalimumab (Humira) for the following indication in adults:

1) reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. In this supplemental Biological License Application (sBLA), the Sponsor pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy. Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses of ulcerative colitis and inflammatory bowel disease.

The Applicant presents data from three phase 3 studies were included in this submission: M06-826 (the pivotal induction study), M06-827 (the pivotal maintenance study), and M10-223 (long-term single-arm, open-label trial that enrolled 498 patients). The endpoints for the two submitted pivotal trials are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤ 2 with no individual subscore >1.

Study M06-826 has an 8- or 12-week randomized, double-blind, placebo-controlled period which is followed by open-label treatment through Week 52. The objective was to evaluated adalimumab for the effectiveness of induction treatment. The study enrolled 576 subjects. The primary endpoint was clinical remission per Mayo score which is defined as total Mayo score ≤ 2 and no individual subscore > 1. (Mayo Score is a composite sore of UC disease activity ranging from 0 to 12 based on the sum of 4 sub scores. The higher the score is, the more severe the disease is. The four sub-scores include endoscopy, stool frequency, rectal bleeding and physician's global assessment.) Week 8 remission rate was 9.2% in the placebo arm and 18.5% in the adalimumab 160/80/40 arm (P=0.031). The adalimumab low dose arm (80/40/40) had a 10.0% clinical remission rate at week 8 which was not significantly different from placebo (P=0.833).

Study M06-827 is a 52-week randomized, double-blind, placebo- controlled, multicenter study which evaluated adalimumab for the effectiveness of induction and maintenance treatment. The study enrolled 518 subjects. The ranked co-primary efficacy endpoints were the

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proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52. Week 8 remission rate was achieved by 9.3% of subjects in the placebo arm and 16.5% of subjects in the adalimumab 160/80/40 arm (P=0.019). Week 52 remission was achieved in 8.5% of subjects in the placebo arm and 17.3% of subjects in the adalimumab 160/80/40 arm (P=0.004).

Study M10-223 evaluated the long-term maintenance of response, safety and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827.

The concerns with this application involve the marginal efficacy noted in Study M06-826 and 827. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject. I am concerned that the clinical development program lacks adequate justification of the balance of risk and benefit of adalimumab treatment for the induction and maintenance of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Given the known serious risks associated with the use of Humira, the data presented in the current Application do not adequately demonstrate that Humira has clinically meaningful efficacy. Further, the results of the submitted studies show that the benefit of Humira for reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy does not outweigh the risks. Given the small treatment effect and E-R analysis results suggest that higher dose may achieve greater treatment effect [for induction], the sponsor should explore higher doses for inducing remission in a clinical trial that define an appropriately labeled dose related to clinical efficacy of Humira. Without an appropriately defined dose, the benefit-risk assessment for Humira may not be favorable, a conclusion that is supported by the fragility of the data. This conclusion is demonstrated through sensitivity analyses revealing that Study M06-826 could be a "negative" study, if a change in the responder status of 1 subjects in the adalimumab 160/80/40 group from responder to non-responder, or in the responder status of just 1 placebo subject from non-responder to responder. This impacts the interpretation of the benefit risk assessment relative to the differences in improvement in clinical remission rates reported (treatment difference in clinical remission at Week 8 of 9.3% and 7.2% in Studies 826 and 827, respectively and treatment difference in sustained clinical remission at Weeks 8 and 52 of 4.4% in Study 827), in light of the known risks of Humira (such as malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome).

Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated

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with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications.

In summary the data in this application do not establish that adalimumab is effective and safe for the treatment of patients with moderately to severely active ulcerative colitis. I have concluded that there is not sufficient evidence of clinical benefit, which coupled with some concerns of safety, makes it impossible for me to justify the marketing of this product without additional key information. The decision to provide a complete response will be supplemented by convening an advisory committee in March 2012 to address a path forward. The data herein submitted yield a Complete response regarding this application.

2. Background

The reader is referred to Dr. Peterson's Clinical Review for further discussion of the regulatory history concerning Humira. Briefly, HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. In this supplemental Biological License Application (sBLA), the applicant pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

3. CMC

The reader is referred to the CMC Review by Jun Park. The CMC Reviewer noted that the Clinical Pharmacology Reviewer raised a concern about the sensitivity of both AAA assays to product interference (i.e., neither the original nor the new AAA assay is able to appropriately measure AAA because of product interference) (see Section 5.1 of this CDTL Review). The CMC Reviewer concluded that an assay with improved drug tolerance should be developed. The following deficiency is included in the CRL:

> "The immunogenicity assay was not adequate. Develop, qualify and implement an improved validated anti-adalimumab antibody (AAA) assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patients samples collected from clinical studies should be banked under appropriate storage conditions."

4. Nonclinical Pharmacology/Toxicology

No new review issues are identified and no nonclinical issues were raised.

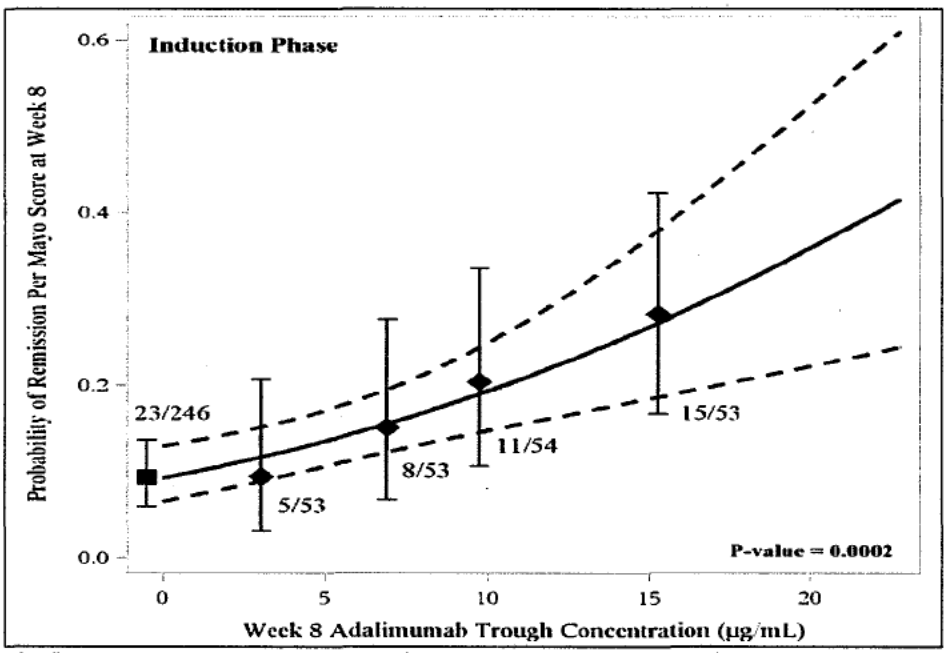
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5. Clinical Pharmacology/Biopharmaceutics

I share my agreement regarding concerns of Dr. Zhou's review that there are significant concerns regarding the lack of complete understanding of the exposure response relationship of adalimumab in inducing and maintaining remission in patients with moderately active to severe ulcerative colitis. The exposure-response analysis conducted based on data from Study M06-827 suggested a higher induction dose might achieve a greater treatment effect for the induction of clinical remission at Week 8. The Clinical Pharmacology Reviewer stated that this conclusion is mainly based on two observations as summarized by Dr. Rajpal:

1) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression. The figure below demonstrates the exposure-response relationship for clinical remission at Week 8 suggesting that higher exposures may be associated with a higher clinical remission rate. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Multivariate logistic regression was performed to determine if the relationship between Week 8 adalimumab trough concentration and Week 8 clinical remission was confounded by baseline Mayo score and prior anti-TNF exposure. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant (p=0.0003).

Figure 1. Logistic Regression Model of the Probability of Remission per Mayo score at Week 8 as a function of Week 8 Adalimumab Trough Concentrations.



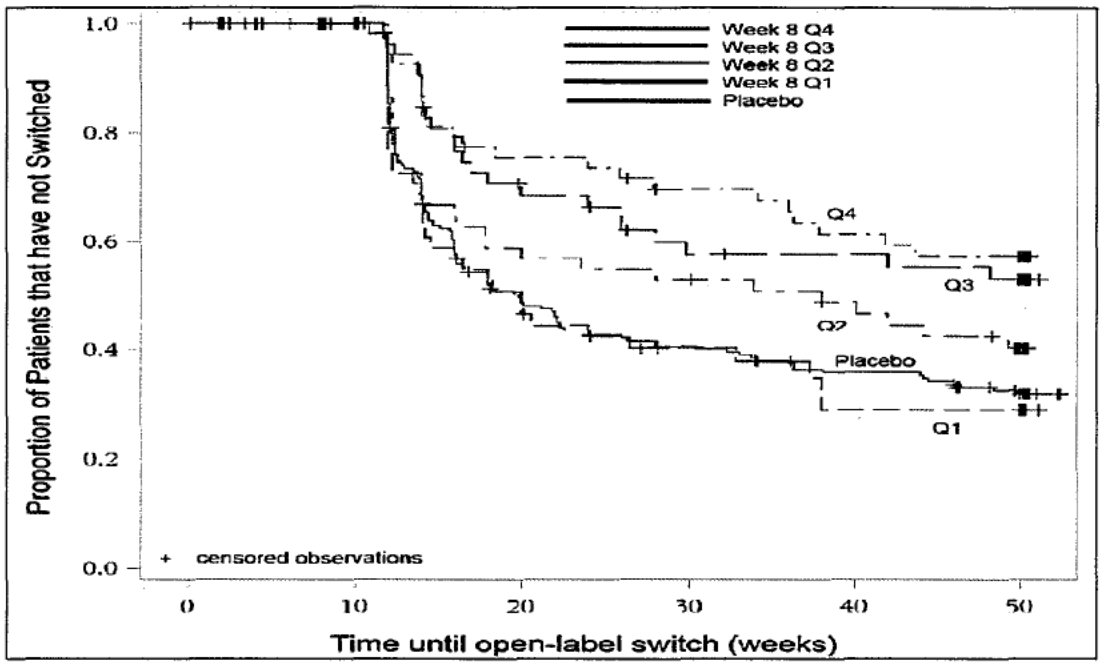
The figure above is taken from Page 17 of the Clinical Pharmacology Review by Lin Zhou.

As a follow up concern, patients with lower exposures in the induction phase were unable to maintain response and switched to open-label treatment earlier than patients with higher

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exposures. The figure below demonstrates that subjects who had lower Week 8 adalimumab trough concentrations lost response earlier than the subjects with higher Week 8 concentrations. This provides additional evidence that exposures achieved by the 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that Week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy at baseline and baseline Mayo score.

Figure 2. Kaplan-Meier Plot of the Proportion of Subjects who have Not Switched vs. Week 8 Adalimumab Trough Concentration Quartile*



***Censored observations are indicated by the "+" symbol.**

The figure above is taken from Page 18 of the Clinical Pharmacology Review by Lin Zhou.

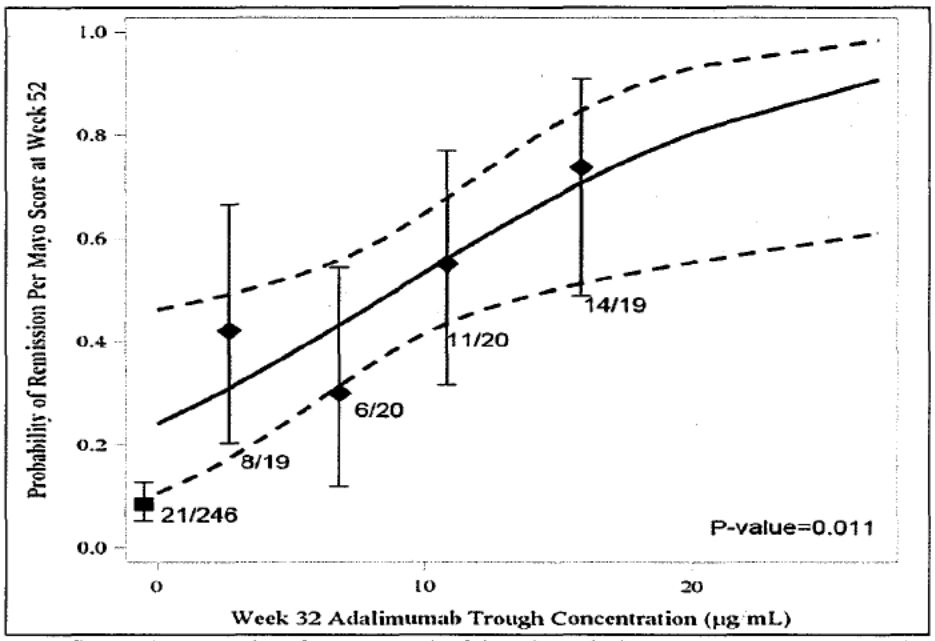
Maintenance Phase:

The Clinical Pharmacology Reviewer concluded that a robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Although the model relating steady state adalimumab trough concentrations to Week 52 remission demonstrates a weak trend in exposure-response (p=0.01, see figure below), suggesting a higher dose may provide additional benefit, the analysis is based on only 78 patients (31% of the total treatment population) who remained in the double-blind phase throughout the trial and had PK data. Other limitations noted by the Clinical Pharmacology Reviewer included the following: (a) The analysis dataset included non-remitters at Week 8. (b) Only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline Mayo score and prior anti-TNF use. (c) The data used in this analysis may not be representative of the actual treatment population since the clinical remission rate is 33% (43/132) for patients who remained in the double-blind

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treatment phase compared to 50% (39/78) for subjects who remained in double blind phase and had PK data.

Figure 3. Logistic Regression Model of the Probability of Remission per Mayo Score at Week 52 as a Function of Week 32 Adalimumab Trough Concentrations.



The figure above is taken from Page 19 of the Clinical Pharmacology Review by Lin Zhou.

In addition there is lack of understanding the impact of Immunogenicity on Adalimumab Pharmacokinetics. No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only very small number of subjects had confirmed antibody status. The assessment of immunogenicity incidence was not adequate in the current submission. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration (≥2 mcg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients. Dr. Zhou states: "Our exposure-response analysis indicates that the dosing has not been fully explored. Without a better defined dosing paradigm the clinical efficacy of Humira in this population can not be considered adequately defined. No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because majority of the subjects in the phase 3 studies were not tested for anti-adalimumab antibodies due to drug interference. In order to obtain an adequate adalimumab immunogenicity profile, we recommend that the Sponsor (1) develop an assay with improved drug tolerance to allow detecting anti-adalimumab antibodies in the presence of adalimumab drug concentration in the study samples collected from patients during treatment, and/or 2) collect post-dose samples at time points where the adalimumab drug concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL)." From a Clinical Pharmacology perspective, the combination of a lack of adequate dose-response combined with a lack of adequate

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immunogenicity information will limit our ability to write adequate labeling with regards to the use of this product.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Humira is not an antimicrobial agent.

7. Clinical/Statistical-Efficacy

The reader is referred to Dr. Rajpal's CDTL memorandum for further review and complete information of historical efficacy and safety data related to clinical trial and exposure data related to adalimumab. Dr. Rajpal recommends a Complete Response to this application for the reasons stating: "Your submission does not provide substantial evidence to establish the efficacy of Humira for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. To address this deficiency, we recommend that you provide additional evidence of efficacy from either: (a) comprehensive re-analyses of outcome data from the clinical trials you have already conducted with Humira; or (b) additional adequate and well-controlled trial(s)." It is my decision that the Agency plans to discuss the efficacy data presented in this application at a future meeting of the Gastrointestinal Drugs Advisory Committee

I do not agree that conduct of comprehensive re-analyses of outcome data would adequately address the deficiency. Given the known serious risks associated with the use of Humira, the data presented in the current application do not adequately demonstrate that Humira has clinically meaningful efficacy. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject. This impacts the interpretation of the benefit risk assessment relative to the differences in improvement in clinical remission rates reported (treatment difference in clinical remission at Week 8 of 9.3% and 7.2% in Studies 826 and 827, respectively and treatment difference in sustained clinical remission at Weeks 8 and 52 of 4.4% in Study 827) and the known risks of Humira (such as malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome).

The data in this application do not allow the establishment of a favorable benefit risk assessment for adalimumab for the treatment of patients in reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. Despite the contrast to already approved medications for the same indication, it is important to understand that there

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there are limitations associated with the use of cross study comparisons. The data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indication. The marginal differences in efficacy observed with adalimumab and the fragility ofnthe data as determined by sensitivity analyses leads to conclude that this application should receive a Complete Response.

It is my conclusion to defer to the counsel of the forthcoming 2012 Advisory Committee that will discuss this application as discussed above and in the Risk Benefit assessment at the conclusion of this memorandum. The Advisory Committee is being asked to comment on the clinical significance of the marginal differences exhibited in efficacy differences between adalimumab and placebo and the corresponding determination of benefit and risk with this application.

8. Safety

The reader is referred to Dr. Peterson's Clinical review and summary by Dr. Rajpal for review of safety issue. There are known serious adverse events associated with the use of Humira. These known risks include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome.

The Clinical Reviewer concluded that there was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies.

9. Advisory Committee Meeting

An Advisory Committee meeting will be convened in March 2012 to address the path forward for this application. In my opinion the clinical development program did not support the benefit outweighing the risk of adalimumab treatment for the induction and maintenance of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy, an advisory committee is necessary to identify future path. Given the small treatment effect and E-R analysis results suggest that higher dose may achieve greater treatment effect [for induction], the sponsor should explore higher doses for inducing remission in a clinical trial. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications.

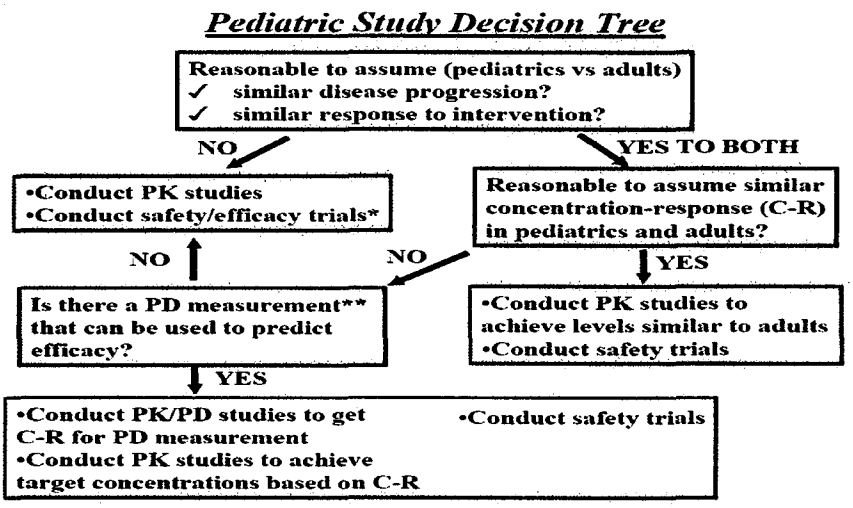
In summary the data in this application do not establish that adalimumab is effective and safe for the treatment of patients with moderately to severely active ulcerative colitis. I have concluded that there is not sufficient evidence of clinical benefit, which coupled with some concerns of safety, makes it impossible for me to justify the marketing of this product without additional key information. The decision to provide a complete response will be supplemented by convening an advisory committee in March 2012 to address a path forward. The data herein submitted do not allow me to make a final decision regarding this application.

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10. Pediatrics

The Pediatric clinical development program would need to validate appropriate endpoints for study in children with moderately to severe ulcerative colitis. The lack of complete understanding the identification of an effective dose of adalimumab in adults would preclude the adoption of extrapolation to children with moderately to severe UC. The role of pharmacokinetics in pediatric clinical trials is discussed in the FDA guidance **Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications**[1]. The Pediatric Study Decision tree from the FDA exposure relationship guidance depicts the role of PK and PD in the development of pediatric clinical trials (see below, excerpted from guidance).

APPENDIX B: PEDIATRIC DECISION TREE INTEGRATION OF PK-PD



From the recent Advisory committee of Remicade in ulcerative colitis (*Gastrointestinal Drugs Advisory Committee (GIDAC)* Hilton Washington DC/Silver Spring, Silver Spring, Maryland **July 21, 2011** ***Summary Minutes)***, it is was deemed to be reasonable to extrapolate efficacy from adults with properly conducted clinical trials based on the assumption that the course of ulcerative colitis and its response to treatment in adult and pediatric patients are sufficiently similar to be able to extrapolate efficacy from adult to pediatric patients. *The committee unanimously agreed that there was sufficient and well supported data to extrapolate from adult to pediatric patients for the induction of clinical remission.* In this case the issue is moot and will need to be discussed post AC for adults.

11. Other Relevant Regulatory Issues

Other issues include the lack of QT evaluation for adalimumab as discussed by Dr. Rajpal, but absence of preclinical concerns or post marketing experience precludes the need for further testing. Additionally a site inspection was conducted at 1 site. For further details, the reader is referred to the CDTL memorandum.

[1] http://www.fda.gov/cder/guidance/index.htm

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12. Labeling

Given that an Approval action is not being planned for this review cycle and there were no labeling negotiations with the Applicant, considerations regarding specific labeling issues are being deferred until the application is otherwise approvable. No DDMAC comments have been provided on labeling.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

Drs. Peterson and Rajpal recommended the product for complete response for which this Signatory concurs with this recommendation. The review of this application has identified a number of deficiencies to be communicated to the Applicant including the following with the reasons for this action and, where possible, our recommendations to address these issues:

CLINICAL

1. Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are two-fold. First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Second, we are concerned that you may not have adequately selected an appropriate adalimumab dose for your pivotal efficacy trials. We note the modest improvement in clinical remission rates reported in both trials (treatment differences relative to placebo in clinical remission at Week 8 of 9.3% and 7.2% in Studies M06-826 and M06-827, respectively), and the treatment difference relative to placebo in sustained clinical remission (at both Weeks 8 and 52) of 4.4% in Study M06-827 and the known risks of Humira (such as malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome).

To address these issues, we will need to seek expert advice regarding the dose, efficacy and overall benefit/risk assessment of Humira for treatment of adult patients with moderately to severely active ulcerative colitis at a future meeting of the Gastrointestinal Drugs Advisory Committee.

IMMUNOGENICITY

2. The immunogenicity assay was not adequate because the original and new immunogenicity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. Therefore, there is a need to develop an assay with better drug tolerance.

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To address this issue, you should develop, qualify and implement an improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patient samples collected from clinical studies should be banked under appropriate storage conditions.

3. The immunogenicity profile for adalimumab has not been adequately assessed.

Utilizing a validated AAA assay as described in Item #2 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay.

13.2 Risk Benefit Assessment:

Given the known serious risks associated with the use of Humira, the data presented in the current Application do not adequately demonstrate that Humira has clinically meaningful efficacy. The data in this application do not allow the establishment of a favorable benefit risk assessment for adalimumab for the treatment of patients in reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is currently approved for the same indications as those proposed for Humira and the two drug products have very similar safety profiles. While there are limitations associated with the use of cross study comparisons, the data from the Remicade approval studies and NNT analyses suggest that Remicade is more efficacious than Humira for the proposed UC indications.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

There are no requirements for postmarketing evaluation.

Recommendation for other Postmarketing Requirements and Commitments

Since this sBLA is not recommended for Approval during this review cycle, recommendations for postmarketing required pediatric studies and postmarketing commitments will be made should this sBLA receive an Approval action during a subsequent review cycle.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

OFFICER/EMPLOYEE LIST

Officer/Employee List
BLA 125057/232

Name	Discipline
Andrew Mulberg	Deputy Director – Division Signatory
Kevin Bugin	RPM
Klaus Gottlieb	Medical Reviewer
Wes Ishihara	CPMS
Jeanne Delasko	SEALD
Yow-Ming Wang	Clin Pharm TL
Laurie Burke	SEALD Director
Lubna Merchant	DMEPA
Eric Brodsky	SEALD
Nitin Mehrotra	Pharmacometrics TL
Jun Park	OBP/DMA
Kevin Krudys	Pharmacometrics
Lin Zhou	Clin Pharm Reviewer
Aisha Peterson-Johnson	Medical Reviewer
Sharon Mills	Patient Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 28, 2012
From	Anil Rajpal, MD, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	BLA 125057/232
Applicant	Abbott Laboratories
Date of Submission	March 30, 2012
PDUFA Goal Date	September 28, 2012
Proprietary Name / Established (USAN) names	Humira® / Adalimumab
Dosage forms / Strength	▪ single-use pen: 40 mg (0.8 mL) ▪ single-dose prefilled glass syringe: 20 mg (0.4 mL); 40 mg (0.8 mL)
Proposed Indication	achieving clinical remission in patients with moderately to severely active UC
Recommended Action:	Approval

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1. Introduction

This application was initially submitted as an efficacy supplement to the BLA (sBLA) for Humira (adalimumab) on January 25, 2011. A Complete Response (CR) Letter was sent by the Division on November 21, 2011. This resubmission, received March 30, 2012, is a complete response to the CR letter, and represents the second review cycle for this sBLA.

Proposed Indication: The proposed indications for ulcerative colitis (UC) in the initial submission and in the current resubmission are each shown below (emphasis added):

- Initial submission: "…for reducing signs and symptoms, and ***inducing and maintaining induction of clinical remission*** in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy."
- Current resubmission: "…for reducing signs and symptoms, and ***achieving clinical remission*** in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy."

Proposed Dose Regimen: The proposed dose regimen for the UC indication is 160 mg initially on Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15), followed in turn by a maintenance dose of 40 mg every other week beginning two weeks later (Day 29). It should be noted that this is the same dose regimen as that for the Crohn's disease indication.

Other Proposed Label Revisions: The Applicant also proposes additions to the Adverse Reactions, Clinical Pharmacology, and Clinical Studies sections.

Advisory Committee Meeting: The application was presented to the Gastrointestinal Drugs Advisory Committee during the current review cycle (August 28, 2012) to seek recommendations on dose selection, demonstration of clinically meaningful benefit, approvability, and need for additional pre-approval and/or post-approval studies. A large majority voted that the optimal dose has not been fully established; they explained that although the optimal dosing has not been fully explored, the dosing regimen studied demonstrated efficacy. A large majority voted that the observed treatment differences for clinical remission at Week 8, clinical remission at Week 52, and clinical remission at both Weeks 8 and 52 each represent a clinically meaningful benefit; in addition, a large majority voted that having clinical remission at Week 52 represents a clinically meaningful endpoint. A large majority voted that pre-approval studies were not necessary. Finally, a large majority voted in favor of approval. There was discussion about post-approval studies; recommendations included exploration of higher doses, evaluation of the relationship between trough concentrations and clinical remission rates, and development of an improved immunogenicity assay.

2. Background

2.1 Humira (adalimumab)

Mechanism of Action: Adalimumab is a recombinant human IgG1 monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors, which in turn inhibits TNFα-induced pro-inflammatory effects.

Other Approved Indications: Humira was originally approved for rheumatoid arthritis in 2002. Since then, it has also been found to be effective in treating several other diseases, and it is currently also approved for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis. The safety and efficacy of Humira in pediatric patients for indications other than juvenile idiopathic arthritis have not been established.

Safety Information: Humira has no specific contraindications. The approved labeling has a boxed warning for serious infections and malignancies, which is part of TNFα-antagonist class labeling. The following serious adverse reactions are highlighted in the boxed warming for serious infections: tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. The following serious adverse reactions are highlighted in the boxed warming for malignancies: hepatosplenic T-cell lymphoma (HSTCL) and other lymphomas and malignancies. There are also warnings and precautions for hypersensitivity reactions, Hepatitis B virus reactivation, demyelinating disease, cytopenias, use with anakinra, heart failure, autoimmunity, use with live vaccines, and use with abatacept.

Dosing Recommendations (Other Approved Indications): The recommended dosing for each of the approved indications is summarized below:

- Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: 40 mg every other week. It should be noted that the labeling states that patients with rheumatoid arthritis who are not receiving concomitant methotrexate may benefit from increasing the dosing frequency to 40 mg every week.
- Juvenile idiopathic arthritis (patients 4 to 17 years of age): 20 mg every other week (for patients that weigh 15 to 30 kg), and 40 mg every week (for patients that weigh 30 kg or more).
- Plaque psoriasis: initial dose of 80 mg followed one week later by a dose of 40 mg every other week.
- Crohn's disease: same dose as that proposed for UC (i.e., 160 mg, followed two weeks later by a dose of 80 mg, in turn followed two weeks later by a dose of 40 mg every other week).

2.2 Ulcerative Colitis

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in

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whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration.

Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population. Surveillance colonoscopies for patients at higher risk are routinely offered.

2.3 Current Treatment Options for Ulcerative Colitis

Decisions about treatment of UC weigh such factors as disease activity, disease extent and duration, previous treatment attempts and the patient's preference. The goal is to stop the patient's active acute disease (induction of remission) and then maintain the patient in remission.

Aminosalicylate preparations, given orally, rectally or in combination, are the first line of treatment for induction of remission (aminosalicylates are approved to treat mildly or moderately active UC including, for certain products, maintenance of remission). Patients with mild-to-moderate UC that is refractory to aminosalicylates are often advanced to oral corticosteroids (approved to "tide the patient over a critical period") and immunosuppressive agents (e.g., azathioprine or 6-mercaptopurine; widely used but unapproved). Use of any of the preceding has come to be considered part of "conventional therapy."

Currently, Remicade (infliximab) is the only TNFα-antagonist approved for induction and maintenance of remission in patients with moderately to severely active UC who have inadequate response to conventional therapy. Remicade has been shown to be effective in this population and has an acceptable safety profile; however, many patients do not respond initially, lose response over time, and/or develop intolerance.

Colectomy is still required for many when medical therapy fails or when epithelial dysplasia is found on surveillance. Total proctocolectomy with ileal pouch–anal anastomosis (IPAA) is currently the procedure of choice because it preserves anal sphincter function. While the mortality of the procedure is low, long-term morbidity is not. Pouchitis, often intermittent and recurrent, is a prevalent problem with symptoms that include increased stool frequency, urgency, incontinence, seepage, and abdominal and perianal discomfort.

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2.4 Regulatory History

The table below summarizes the regulatory activity pertinent to the current efficacy supplement.

Table 1. Pertinent Regulatory History of Humira (sBLA 125057/232)*

Date	Event
June 15, 2006	Pre-IND / Pre-Phase 3 Meeting
September 5, 2008	Advice Letter for Study 826 Statistical Analysis Plan
May 24, 2010	Advice Letter for Study 827 Statistical Analysis Plan
November 23, 2010	Pre-sBLA Meeting
January 25, 2011	**sBLA Original Submission**
November 21, 2011	Complete Response Action
January 25, 2012	End of Review Meeting with Sponsor
March 30, 2012	**sBLA Re-Submission**
August 28, 2012	Gastrointestinal Drugs Advisory Committee Meeting

*IND 100103

Before the Original Submission: Key comments communicated to the sponsor during the meetings and in the advice letters before the original submission included the following:

- Weaknesses of not having a Phase 2 program in UC: The same dose regimen (160/80/40) as that used in the Crohn's disease (CD) program might not be optimal for UC (particularly because there is no PK data to support this dose regimen in UC). Similarly, the Week 8 timepoint for assessing clinical response or clinical remission may not be the optimal choice for UC (see Pre-IND / Pre-Phase 3 Meeting Minutes).
- Number of Induction Studies: Usually two adequate and well-controlled studies are needed to provide substantial evidence of efficacy for an indication for induction (see Pre-IND / Pre-Phase 3 Meeting Minutes).
- Design of Maintenance Study: An indication for "maintenance of clinical remission" would require that patients who are in clinical remission at Week 8 be re-randomized. Re-randomization at the end of the induction phase to drug or placebo allows the separate effect of maintenance therapy to be evaluated. As designed (without re-randomization at Week 8), the study could only support an indication of "sustained clinical remission" at Weeks 8 and 52 (see Advice Letter for Study 827 Statistical Analysis Plan).
- Post Hoc Analysis using Alternate Definition of Clinical Remission: The Division requested the sponsor to conduct a post-hoc sensitivity analysis using the following alternate definition of clinical remission (one more in line with current Division recommendations): total Mayo score of ≤ 2 with rectal bleeding subscore=0 and endoscopy subscore=0 (see Pre-sBLA Meeting Minutes). (The original definition of clinical remission was a total Mayo score of ≤ 2 with no individual subscore >1; see also Appendix 1: Mayo Score.)

Complete Response Letter: Although the two trials submitted in support of the application (Studies 826 and 827) demonstrated statistically significant improvement with Humira relative to placebo, the concerns below were identified in the Complete Response (CR) Letter (dated November 21, 2011):

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- Robustness of Results (Study 826): For Study 826, the conclusions are not considered robust from a statistical perspective because the results are sensitive to alternative analyses. (Specific analyses by the Statistical Reviewer were cited: use of exact testing methods, change in remitter status of one patient in the placebo or Humira group, and adjusting the primary analysis by baseline Mayo score.)
- Dose Selection / Modest Improvements in Clinical Remission Rates (Studies 826 and 827): For both Studies 826 and 827, the appropriate dose may not have been selected. Also, for both studies, the modest improvements in the rates of clinical remission at Week 8 and sustained clinical remission at Weeks 8 and 52 reported (treatment differences relative to placebo) were noted.

The CR Letter also stated that these concerns would be discussed in a future meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC). (See CR Letter in Appendix 2.)

End of Review Meeting: The sponsor discussed their approach in responding to the review issues in the End of Review Meeting (January 25, 2012). The sponsor proposed submitting additional analyses that explore the totality of the data, demonstrate the clinical meaningfulness of the clinical results, and support a favorable benefit/risk profile. The Division advised the sponsor that the resubmission would be accepted for review, but the multiple post hoc analyses proposed would be considered exploratory.

Advisory Committee Meeting: The application was presented to the Gastrointestinal Drugs Advisory Committee during the current review cycle (August 28, 2012) to seek recommendations on: (1) dose selection, (2) efficacy analysis; (3) additional pre-approval studies, (4) benefit-risk considerations, and (5) post-approval studies. The outcome of the meeting was as follows:

(1) Dose Selection: In response to the question of whether the optimal dose has been adequately established, 3 voted yes, and 14 voted no.

(2) Efficacy Analysis: The Committee was asked to discuss the factors they consider in defining "clinically meaningful benefit" in this patient population; considerations included a specific magnitude of difference, steroid-sparing effect, and avoidance of colectomy. The Committee was asked if the observed treatment differences for clinical remission at Week 8, at Week 52, and at both Weeks 8 and 52, were clinically meaningful; the votes were as follows:
   - Week 8: Yes=15 votes; No=1 vote; Abstain=1 vote.
   - Week 52: Yes=16 votes; No=1 vote.
   - Both Weeks 8 and 52: Yes=10 votes; No=6 votes; Abstain=1 vote.

   In addition, the Committee was asked if the endpoint of clinical remission at Week 52 represents a clinically meaningful endpoint; the votes were as follows: Yes=16 votes; No=1 vote.

(3) Additional Pre-Approval Studies: Regarding the question of whether there should be additional efficacy studies prior to approval for moderately to severely active UC, the Committee voted as follows: Yes=3 votes; No=13 votes; Abstain=1 vote.

(4) Benefit-Risk Considerations: Regarding the question of whether the expected benefits outweigh the known and potential risks, the Committee voted as follows: Yes=15 votes; No=2 votes.

(5) Post-Approval Studies: The Committee was asked to discuss studies that should be conducted post-approval if they believe this application should be approved.

Recommendations included exploration of higher doses, evaluation of the relationship between trough concentrations and clinical remission rates, and development of an improved immunogenicity assay.

(Additional details of the Advisory Committee Meeting are provided in Section 9 of this CDTL Review.)

See the Clinical Reviews by Aisha Peterson Johnson (first review cycle) and Klaus Gottlieb (current review cycle) for details of the Humira regulatory history.

2.5 Current Application

The application was received on March 30, 2012. It was classified as a six-month submission with a PDUFA deadline of September 28, 2012.

The application was presented to the Gastrointestinal Drugs Advisory Committee on August 28, 2012.

The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

(1) Clinical Review by Klaus Gottlieb, dated September 28, 2012
(2) Primary Statistics Review by Milton Fan, dated September 24, 2012
(3) Secondary Statistics Review by Mike Welch, dated September 27, 2012
(4) Clinical Pharmacology Review by Kevin Krudys, dated September 17, 2012
(5) Division of Medication Error Prevention and Analysis (DMEPA) Label, Labeling, and Packaging Review by Teresa McMillan dated September 14, 2012
(6) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Sharon Mills dated September 13, 2012
(7) Office of Prescription Drug Promotion (OPDP) Label Review by Kendra Jones dated September 10, 2012
(8) Study Endpoints and Label Development Team (SEALD) Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies by Eric Brodsky dated September 12, 2012

The reviews should be consulted for more specific details of the current application.

3. CMC

3.1 First Review Cycle

The reader is referred to the CMC Review by Jun Park from the first review cycle.

The CMC Reviewer noted that all quality information was submitted under the original BLA for Humira. However, the CMC Reviewer became aware during the first review cycle of this

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sBLA that samples from Study M06-827 (submitted for review in the sBLA) were assayed for serum anti-adalimumab antibody (AAA) using a new immunogenicity method, while samples from Studies M02-403, M04-691 and M02-433 (studies submitted in a previous efficacy supplement for Crohn's disease) were measured for serum AAA using the original immunogenicity method approved under the original BLA.

The CMC Reviewer noted that the Clinical Pharmacology Reviewer raised a concern about the sensitivity of both AAA assays to product interference (i.e., neither the original nor the new AAA assay is able to appropriately measure AAA because of product interference) (see Section 5.1 of this CDTL Review). The CMC Reviewer concluded that an assay with improved drug tolerance should be developed.

The following was included in the CR Letter as an issue to be addressed (but was not considered an approvability issue):

- The immunogenicity assay was not adequate because the original and new immunogenicity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. Therefore, there is a need to develop an assay with improved drug tolerance. To address this issue, you should develop, qualify and implement an improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patient samples collected from clinical studies should be banked under appropriate storage conditions.

(See CR Letter in Appendix 2.)

3.2 Current Review Cycle

There were no new CMC data in the resubmission, and no additional review of CMC data was performed in the current review cycle.

3.3 Final Recommendation

An Approval Action is the final recommendation by CMC.

The issue identified in the first review cycle (need for an improved validated AAA assay with reduced sensitivity to product interference) was deemed not to preclude approval of the application since it could be addressed as a postmarketing requirement (PMR). See PMR #3 in Section 13.5.

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4. Nonclinical Pharmacology/Toxicology

This is a currently marketed product. No new nonclinical study data were presented in this application.

5. Clinical Pharmacology/Biopharmaceutics

5.1 First Review Cycle

The reader is referred to the Clinical Pharmacology Review by Lin Zhou from the first review cycle.

The focus of the Clinical Pharmacology Review was on Study 827 since it was the only study in which pharmacokinetics (PK) and immunogenicity data were collected.

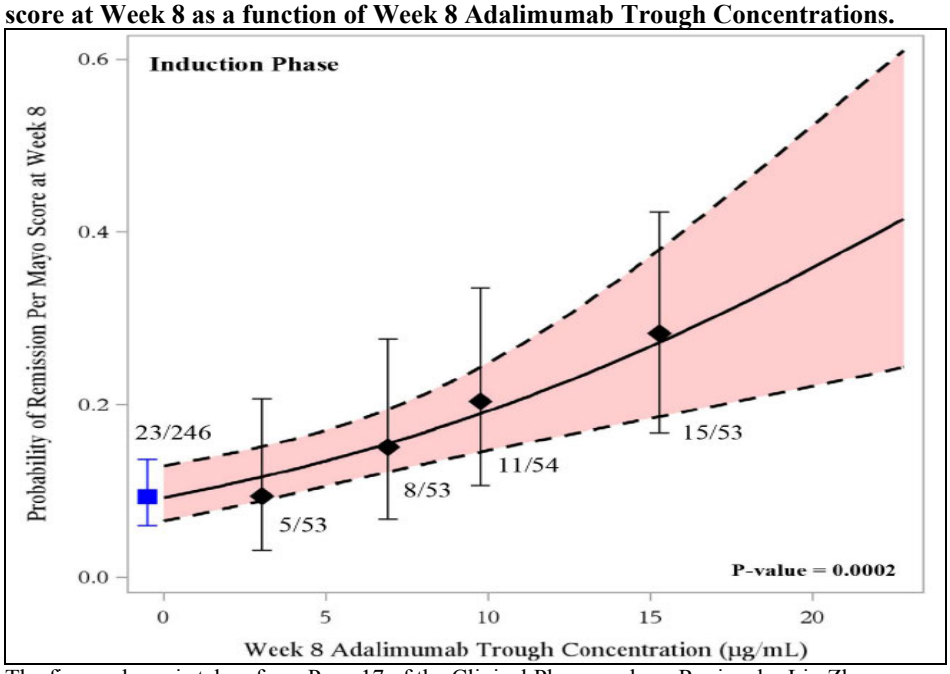
5.1.1 Exposure-Response Analysis

Induction Phase:

The Clinical Pharmacology Reviewer noted that the exposure-response analysis conducted based on data from Study M06-827 suggested a higher induction dose could achieve a greater treatment effect for the induction of clinical remission at Week 8. The Clinical Pharmacology Reviewer stated that this conclusion is mainly based on two observations:

(1) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression. The figure below demonstrates the exposure-response relationship for clinical remission at Week 8 suggesting that higher exposures may be associated with a higher clinical remission rate. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Multivariate logistic regression was performed to determine if the relationship between Week 8 adalimumab trough concentration and Week 8 clinical remission was confounded by baseline Mayo score and prior anti-TNF exposure. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant (p=0.0003).

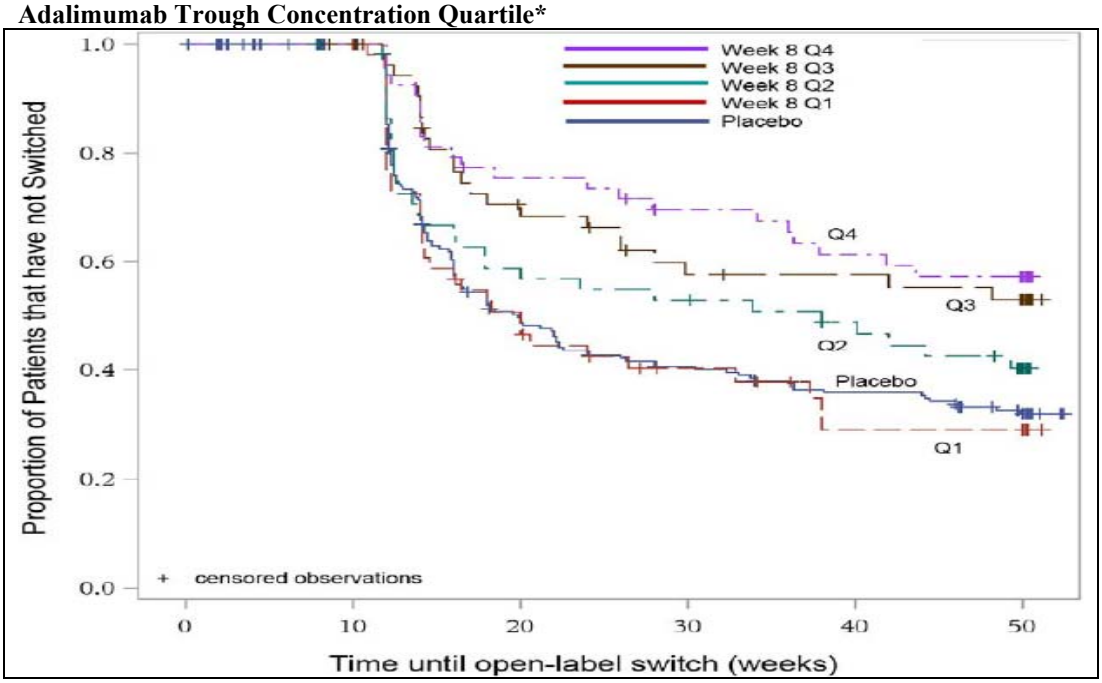
Figure 1. Logistic Regression Model of the Probability of Remission per Mayo score at Week 8 as a function of Week 8 Adalimumab Trough Concentrations.



The figure above is taken from Page 17 of the Clinical Pharmacology Review by Lin Zhou.

(2) Patients with lower exposures in the induction phase were unable to maintain response and switched to open-label treatment earlier than patients with higher exposures. The figure below demonstrates that subjects who had lower Week 8 adalimumab trough concentrations lost response earlier than the subjects with higher Week 8 concentrations. This provides additional evidence that exposures achieved by the 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that Week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy at baseline and baseline Mayo score.

Figure 2. Kaplan-Meier Plot of the Proportion of Subjects who have Not Switched vs. Week 8 Adalimumab Trough Concentration Quartile*

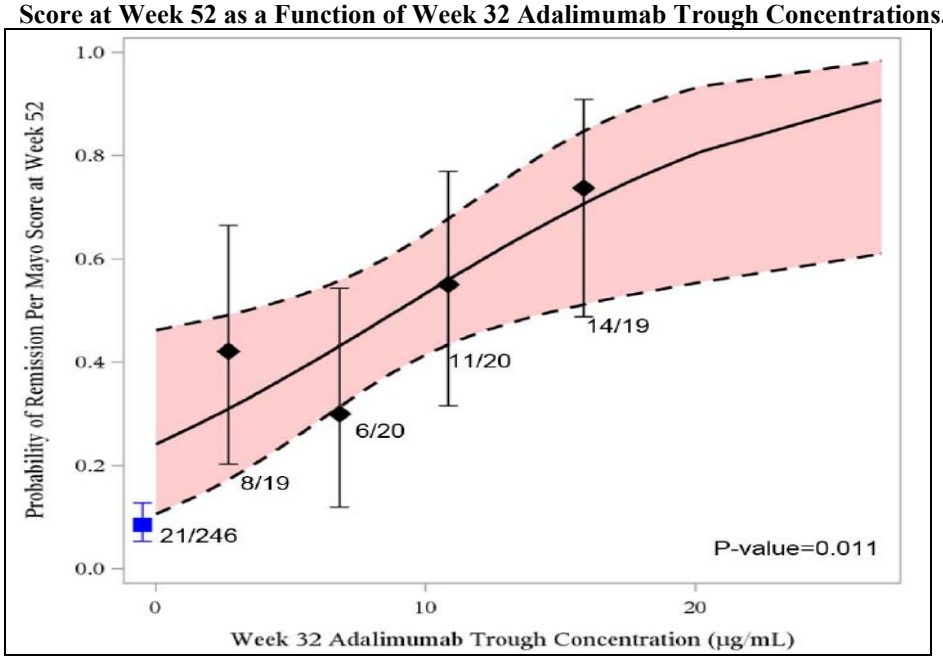


***Censored observations are indicated by the "+" symbol.**
The figure above is taken from Page 18 of the Clinical Pharmacology Review by Lin Zhou.

Maintenance Phase:

The Clinical Pharmacology Reviewer concluded that a robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Although the model relating steady state adalimumab trough concentrations to Week 52 remission demonstrates a weak trend in exposure-response (p=0.01, see figure below), suggesting a higher dose may provide additional benefit, the analysis is based on only 78 patients (31% of the total treatment population) who remained in the double-blind phase throughout the trial and had PK data. Other limitations noted by the Clinical Pharmacology Reviewer included the following: (a) The analysis dataset included non-remitters at Week 8. (b) Only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline Mayo score and prior anti-TNF use. (c) The data used in this analysis may not be representative of the actual treatment population since the clinical remission rate is 33% (43/132) for patients who remained in the double-blind treatment phase compared to 50% (39/78) for subjects who remained in double blind phase and had PK data.

Figure 3. Logistic Regression Model of the Probability of Remission per Mayo Score at Week 52 as a Function of Week 32 Adalimumab Trough Concentrations.



The figure above is taken from Page 19 of the Clinical Pharmacology Review by Lin Zhou.

5.1.2 Immunogenicity

The Clinical Pharmacology Reviewer stated that no conclusions could be drawn regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only a small proportion of subjects had confirmed antibody status. The assessment of immunogenicity incidence was not adequate. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration (≥ 2 mcg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients.

The Clinical Pharmacology Reviewer concluded that an assay with improved drug tolerance should be developed (see Section 3.1 of this CDTL Review) and/or post dose AAA samples should be collected at time points when the adalimumab concentrations would not be expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL).

The following was included in the CR Letter as an issue to be addressed (but was not considered an approvability issue):

- The immunogenicity profile for adalimumab has not been adequately assessed. Utilizing a validated AAA assay as described in Item #1 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay.

Note that "Item #1" above refers to the item from CMC; see Section 3.1. (See CR Letter in Appendix 2.)

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5.2 Current Review Cycle

The Clinical Pharmacology Review concluded that the contents of the resubmission do not change the conclusions of the original review. The reader is referred to the current review cycle Clinical Pharmacology Review for complete information.

5.3 Final Recommendation

The immunogenicity issue identified in the first review cycle (need for an assessment of the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay) was deemed not to preclude approval of the application since it could be addressed as a PMR. See PMR #4 in Section 13.5.

Because the exposure-response analysis suggested that a higher induction dose would lead to a higher treatment effect, the Clinical Pharmacology Reviewers recommended a PMR to study a higher induction dose. See PMR #5 in Section 13.5.

The Clinical Pharmacology and Clinical Reviewers agreed that there should be a PMR for a trial to address the concern of serious adverse events (SAEs) in patients receiving higher doses of Humira (because their physicians escalate the dose in response to loss of remission); the trial will evaluate trough concentrations and antibody levels at the time of loss of clinical remission and will evaluate if patients with low exposures benefit from an escalation of the dose without increasing the risk of SAEs. See PMR #6 in Section 13.5.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Humira is not an antimicrobial agent.

7. Clinical/Statistical - Efficacy

7.1 First Review Cycle

An overview of the clinical/statistical efficacy issues from the first review cycle is presented below.

For complete information, the reader is referred to the following reviews from the first review cycle: CDTL Review by Anil Rajpal, Clinical Review by Aisha Peterson Johnson, and Statistics Review by Milton Fan.

7.1.1 Clinical Studies

The table below summarizes the two controlled clinical trials (Studies 826 and 827) and one open label clinical trial (Study 223) submitted in support of the sBLA.

Table 2. UC Studies

Study	Design	Population	Treatment Duration	Treatment Arms
826 (Induction of Remission Trial)	R, DB, PC	▪ Moderately to severely active UC*	8 weeks	➢ Humira 160/80/40[#] (n=130[‡]) ➢ Humira 80/40[†] (n=130[‡]) ➢ Placebo (n=130[‡])
827 (Induction and Sustained Remission Trial)	R, DB, PC	▪ Moderately to severely active UC* ▪ Prior TNFα-antagonist users (40%)	52 weeks	➢ Humira 160/80/40[#] (n=258) ➢ Placebo (n=260)
223 (Extension Study)	OL	▪ Continuation from Studies 826 and 827	240 weeks planned (ongoing)	➢ Humira 40 EOW or EW (n=592[§])

R: Randomized; DB: Double-blind; PC: Placebo-controlled
*Total Mayo Score ≥ 6 and Endoscopy sub-score ≥ 2 despite concurrent or prior treatment with steroids and/or immunosuppressants.
[#] 160/80/40: 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and every other week (EOW) thereafter;
[†] 80/40: 80 mg at Week 0, 40 mg at Week 2, and EOW thereafter;
[‡] n indicates ITT-A3 pre-specified analysis population (after Amendment 3: addition of a third lower dose treatment arm).
[§] Data cutoff date of December 16, 2011. 592 enrolled (349 receiving 40 mg EOW and 243 receiving 40 mg EW); 384 ongoing (255 receiving 40 mg EOW and 129 receiving 40 mg EW); escalation from EOW to EW allowed during study for inadequate response.

Both studies enrolled patients with a Total Mayo Score of ≥ 6 and Endoscopy sub-score of ≥ 2 despite concurrent or prior treatment with steroids and/or immunosuppressants.

Prior TNFα-Antagonist Use: The proposed indicated population is limited to patients that had an inadequate response to conventional therapy (where conventional therapies include mesalamine, immunosuppressants and steroids). Although both studies enrolled patients that met these criteria, the two studies differed on criteria for prior TNFα-antagonist use. In one study, all patients were naïve to prior TNFα-antagonists while in the other study approximately 40% of patients enrolled had lost response to or were intolerant to a prior TNFα-antagonist. See table below.

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Table 3. Prior TNFα-Antagonist Use by Study

Study	Prior TNFα-Antagonist Use Criteria
826 (Induction of Remission Trial)	Excluded patients that previously used a TNFα-Antagonist
827 (Induction and Sustained Remission Trial)	Allowed entry of patients that previously used a TNFα-Antagonist provided they discontinued due to a **loss of response* or intolerance**[#] to the agent.

*Loss of Response: responded previously to a TNFα-antagonist but lost response after at least 2 subsequent doses
[#] Intolerance defined as acute or delayed reaction.

Primary Endpoints: The primary endpoints are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤2 with no individual sub-score >1.

Table 4. Primary Endpoint by Study

Study	Primary Endpoint
826 (Induction of Remission Trial)	**Clinical Remission at Week 8**
827 (Induction and Sustained Remission Trial)	Ranked Co-Primary Endpoint: (1) **Clinical Remission at Week 8** (2) **Clinical Remission at Week 52**

Study 827 was the only study submitted to support the proposed indication for maintenance of remission. It should be noted that a study design intending to support maintenance of remission should re-randomize subjects that achieve remission at Week 8. Re-randomization at the end of the induction phase to drug or placebo allows the separate effect of maintenance therapy to be evaluated. The design of Study 827 is better suited to support sustained remission (a measure of durability in contrast to maintenance); i.e., if the ranked co-primary endpoint and the first-ranked secondary endpoint of sustained remission (**Clinical Remission at Weeks 8 and 52**) are met.

7.1.2 Efficacy Results

Induction of Clinical Remission and Sustained Clinical Remission:

The results for the primary endpoints of Studies 826 and 827 and the first-ranked secondary endpoint of Study 827 are shown in the table below.

Table 5. Clinical Remission (Studies 826 and 827)

Study Week	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	95% CI	p-value[‡]
Study 826					
Week 8*	9.2% (12/130)	18.5% (24/130)	**9.3%**	**(0.8%, 17.9%)**	**0.031**
Study 827					
Week 8[#]	9.3% (23/246)	16.5% (41/248)	**7.2%**	**(1.3%, 13.2%)**	**0.019**
Week 52[#]	8.5% (21/246)	17.3% (43/248)	**8.8%**	**(2.9%, 14.8%)**	**0.004**
Weeks 8 and 52[†]	4.1% (10/246)	8.5% (21/248)	**4.4%**	**(0.1%, 9.0%)**	**0.047**

*Clinical Remission at Week 8 is the Primary Endpoint of Study 826.
[#]Clinical Remission at Week 8 is the first ranked Co-Primary Endpoint of Study 827; Clinical Remission at Week 52 is the second ranked Co-Primary Endpoint of Study 827.
[†]Clinical Remission at Weeks 8 and 52 is the first-ranked secondary endpoint of Study 827.
[‡] Based on the chi-squared test for Study 826 and the Cochran-Mantel-Haenszel (CMH) test for Study 827

Secondary Endpoint Results:

In Study 826, there was a lack of supportive evidence from secondary endpoint results. The Statistical Reviewer noted that the first ranked secondary endpoint (clinical response per Mayo score at Week 8) in Study 826 was not statistically significant (see the table below).

Table 6. First-Ranked Secondary Endpoint (Study 826)

	Placebo	Humira 160/80/40	p value
Clinical Response at Week 8	58/130 (44.6%)	71/130 (54.6%)	0.107

Table above modified from the Clinical Review from the First Review Cycle.

Study 827 did have supportive evidence from secondary endpoint results. The first eight ranked secondary endpoints had statistically significant results (see the table below).

Table 7. First Nine Ranked Secondary Endpoints, Study 827

Ranked Secondary Endpoint		Placebo N=246	Humira 160/80/40 N=248	p-value
1	Sustained remission, Week 8 and Week 52	4.1% (10)	8.5% (21)	0.047
2	Response, Week 8	34.6% (85)	50.4% (125)	<0.001
3	Response, Week 52	18.3% (45)	30.2% (75)	0.002
4	Sustained Response, Week 8 and Week 52	12.2% (30)	23.8% (59)	<0.001
5	Mucosal healing, Week 8	31.7% (78)	41.1% (102)	0.032
6	Mucosal healing, Week 52	15.4% (38)	25.0% (62)	0.009
7	Sustained Mucosal healing, Week 8 and Week 52	10.6% (26)	18.5% (46)	0.013
8	Discontinued corticosteroid use before Week 52 and achieved remission, Week 52	5.7% (8)	13.3% (20)	0.035
9	PGA (physician's global assessment) ≤1, Week 8	37.4% (92)	46.0% (114)	0.058

Study 827, CSR p 354/3632

Subgroup Analysis by Prior TNFα-Anatagonist Use (Study 827)

Induction of clinical remission (clinical remission at Week 8), sustained clinical remission (clinical remission at both Weeks 8 and 52), and clinical remission at Week 52 results are shown in the table below in subgroups based on prior TNFα-antagonist use in Study 827.

Table 8. Subgroup Analysis Based on Prior TNFα-antagonist use (Study 827)

	No Prior TNFα-antagonist Use			Prior TNFα-antagonist Use		
	Placebo	Humira 160/80/40	Δ	Placebo	Humira 160/80/40	Δ
Clinical Remission at Wk 8	11.0% (16/145)	21.3% (32/150)	10.3%	6.9% (7/101)	9.2% (9/98)	2.3%
Clinical Remission at Both Wks 8 and 52	6.2% (9/145)	10.7% (16/150)	4.5%	1.0% (1/101)	5.1% (5/98)	4.1%
Clinical Remission at Wk 52	12.4% (18/145)	22.0% (33/150)	9.6%	3.0% (3/101)	10.2% (10/98)	7.2%

CSR Study 827, p254/3632

A numerically lower treatment difference for induction of clinical remission was observed in the prior TNFα-antagonist use subgroup than in the no prior TNFα-antagonist use subgroup. Similar treatment differences for sustained clinical remission and for clinical remission at Week 52 were observed in the prior TNFα-antagonist use subgroup and the no prior TNFα-antagonist use subgroup.

7.1.3 Approvability Issues Identified (First Review Cycle)

In CR Item #1, concerns about the robustness of results (Study 826) and dose selection / modest improvements in clinical remission rates (both Studies 826 and 827) were described. (See CR Item #1 in Appendix 2.)

Item #1: Robustness of Results (Study 826)

Sensitivity analyses conducted by the Statistical Reviewer led to the concern that the results of Study 826 are not robust from a statistical perspective (see CR Letter Item #1 in Appendix 2). These analyses are summarized below.

Table 9: Alternative Analyses (Study 826 Primary Endpoint)

Alternative Analyses	Placebo	Humira 160/80/40	Humira-Placebo	p-value
Original Analysis* (for reference)	9.2%	18.5%	9.3%	0.031
#1: Fisher's Exact Test (instead of Chi-squared)	9.2%	18.5%	9.3%	**0.047**
#2a: One Humira Patient Changed from Remitter to Non-Remitter#	9.2%	17.7%	8.5%	**0.068**
#2b: One Placebo Patient Changed from Non-Remitter to Remitter#	10.0%	18.5%	8.5%	**0.075**

*The original analysis used the chi-squared test and did not adjust for baseline Mayo scores
#This analysis used Fisher's exact test

Note that for #1, the p value becomes borderline, and that for #2a and #2b, the p value becomes non-significant. In addition to the above, adjusting the primary analysis for the significantly different baseline Mayo scores (see Appendix 3), the treatment difference was not statistically significant (p=**0.085**).

Item #1 (cont.): Dose Selection / Modest Improvements in Remission (826 and 827)

The Clinical Reviewer questioned whether the treatment differences of less than 10% for induction of clinical remission observed in both studies and less than 5% for sustained clinical remission observed in Study 827 are clinically meaningful. The Clinical Reviewer questioned if the results could be related to the dose selected for the clinical trials (see also Section 5.1.1 Clinical Pharmacology – Exposure-Response Analysis). In addition, although there are limitations of cross-study comparisons, the Clinical Reviewer noted that the treatment differences observed were numerically lower than those observed for Remicade, the only currently approved TNFα-antagonist product for UC.

The CR Letter Item #1 stated that the applicant may not have selected an appropriate dose, that the treatment differences (for induction of clinical remission and sustained clinical remission) were modest, and that expert advice would be sought at a future meeting of the GIDAC (see CR Letter Item #1 in Appendix 2).

7.1.4 Other Issues Identified (not Approvability Issues) (First Review Cycle)

Items #3 and #4 in the CR Letter (under Statistical) (see Appendix 2) describe other issues identified that are not approvability issues. These are summarized below.

Item #3a: Study 826 Secondary Endpoint Results and Subgroup Analysis by CRP

Secondary Endpoint Results of Study 826: The Statistical Reviewer noted that there was a lack of supportive evidence from the first ranked secondary endpoint (clinical response at Week 8) (see Section 7.1.2).

Inconsistent Treatment Effects in Subgroup Analysis Based on CRP: The Statistical Reviewer noted that there were inconsistent treatment effects in the subgroup analysis based on CRP (see the table below). (See other selected subgroup analyses in Appendix 4.)

Table 10. Subgroup Analysis Based on CRP (Study 826)

Subgroup	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
CRP <10.0 mg/L	7/95 (7.4%)	21/101 (20.8%)	13.4%
CRP ≥10.0 mg/L	4/32 (12.5%)	2/25 (8.0%)	-4.5%

The table above is modified from the First Cycle Clinical Review.

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Item #4a: Study 827 Robustness of Sustained Remission Results and Missing Data

Robustness of Sustained Clinical Remission Results: The Statistical Reviewer noted that the sustained clinical remission endpoint is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062).

Missing Data: The Statistical Reviewer noted that for both the sustained clinical remission endpoint and the clinical remission at Week 52 co-primary endpoint, there were large numbers of early drop-outs (78% placebo vs. 69% adalimumab). These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

Item #4b: Study 827 Subgroup Analysis by Use of Azathioprine or 6-MP at Baseline

Inconsistent Treatment Effects in Subgroup Analysis By Baseline Azathioprine or 6-MP: The Statistical Reviewer noted that a subgroup analysis based on use of azathioprine or 6-MP at baseline (yes vs. no) showed an inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo (see table below). (See other selected subgroup analyses in Appendix 5.)

Table 11. Subgroup Analysis (Remission at Week 8) Azathioprine or 6-MP at Baseline (827)

Azathioprine or 6-MP at Baseline	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%

The table above is modified from the First Cycle Clinical Review.

Item #4c: Study 827 Not Designed to Demonstrate Maintenance of Clinical Remission

The Statistical Reviewer noted that a study design intending to show maintenance of clinical remission should re-randomize patients that achieve induction of clinical remission. The Applicant's first ranked secondary endpoint of sustained clinical remission is a measure of durability in contrast to maintenance.

7.2 Current Review Cycle

The reader is referred to the Clinical Review by Klaus Gottlieb and the Statistical Review by Milton Fan for complete information.

7.2.1 Assessment of Applicant's Response to Approvability Issues (CR Item #1)

A summary of the Clinical/Statistical Reviewers' assessment of the Applicant's response to Item #1 in the CR Letter is presented below. Also, this Reviewer's assessment and the recommendations of the Advisory Committee are included below.

Item #1: Robustness of Results (Study 826)

As part of the response to this item (to address the concern by the Statistical Reviewer that adjusting the primary analysis for the significantly different baseline Mayo scores leads to a treatment difference that was not statistically significant (p=0.085)), the Applicant submitted analyses adjusting for baseline Mayo scores (categorizing by quartiles, by tertiles, and by median) (see table below and Appendix 6).

Table 12. Applicant's Analysis #1: Adjustment for Baseline Mayo Score (Study 826 Primary Endpoint)

Analysis	Description	p-value
Original (for reference)	▪ Did not adjust for Baseline Mayo Score ▪ Used the chi-squared test	0.031
Statistical Reviewer (1st cycle)	▪ Adjusted for Baseline Mayo Score (categorizing by score) ▪ Used the CMH test	0.0852
#1a (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by quartiles)# ▪ Used the CMH test	0.034
#1b (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by tertiles)# ▪ Used the CMH test	0.034
#1c (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by median)# ▪ Used the CMH test	0.028

CMH: Cochran-Mantel-Haenszel
#See Appendix 6

The Statistical Reviewer commented that the additional analyses by the Applicant are alternative ways to adjust for baseline Mayo score but are less sensitive than the Statistical Reviewer's method. Moreover, the Statistical Reviewer considers these results hypothesis generating as the methods of categorization (by quartiles, tertiles, and median) were not pre-specified.

In addition, the Statistical Reviewer is concerned that a single patient in the Humira 160/80/40 arm (Patient # 63,951) may have been misclassified as a remitter; the Reviewer noted that it is still unclear and debatable whether or not that particular patient was correctly classified. However, after receipt of additional clinical information on this case, the Clinical Reviewer concluded that this patient is indeed a remitter (see Clinical Review).

The Statistical Reviewer continues to be concerned about the robustness of results for the Clinical Remission at Week 8 endpoint from Study 826. The Statistical Reviewer also noted that this issue (robustness of results for the Clinical Remission at Week 8 endpoint from Study 826) was not discussed by the Advisory Committee.

This reviewer believes that the Applicant has addressed the concern that results are non-significant after adjustment for baseline Mayo Scores by using the alternate methods for adjustment shown above. However, this reviewer agrees with the Statistical Reviewer that there may still be a concern about the robustness of the Study 826 Week 8 result.

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Item #1 (cont.): Dose Selection / Modest Improvements in Remission (826 and 827)

The Applicant's response to the concern about dose selection is discussed in the Clinical Pharmacology section (see Section 5). The Clinical Pharmacology Reviewer concluded that the exposure-response data (from Study 827) suggested that a higher induction dose would lead to a higher treatment effect. For maintenance, data were not sufficient to determine an exposure-response relationship. In addition, a question about dose selection was posed to the Advisory Committee (see Sections 2.4 and 9); in response to the question of whether the optimal dose has been adequately established, 3 voted yes, and 14 voted no.

The Applicant responded to the concern about the modest treatment differences observed in both studies by providing a number of supplemental and exploratory analyses that included the following:

- primary and secondary analyses of Study 826 using the ITT-E population (i.e., all patients enrolled that received study drug or placebo);
- integrated primary and secondary analyses across Studies 826 and 827;
- additional exploratory analyses from Study 827 (e.g., clinical response based on partial Mayo score at Weeks 2, 4, and 8);
- re-analysis of full and partial Mayo scores at Baseline and Week 52 using average of last 3 days (rather than standard "worst-ranked" methodology)-Study 827;
- exploratory analyses of clinical remission and clinical response status at Week 52 in the subgroup of patients from Study 827 in clinical response at Week 8;
- serious adverse event (SAE)-adjusted days in remission;
- number of patients who discontinued due to adverse events (AEs) relative to number of patients in remission at Weeks 8 and 52;
- Net Efficacy Adjusted Risk (NEAR) analysis; and
- Number Needed to Harm (NNH) analyses.

The supplemental and exploratory analyses were difficult to interpret because many of the endpoints and the precise methods of comparisons were not clearly defined prior to the start of the studies. Thus, although these analyses were included in the Meeting Materials for the Advisory Committee meeting and are included in this CDTL Review (see the Applicant's analyses and discussion in Appendix 7), the Advisory Committee questions and discussion as well as the clinical and statistical reviews focused on the analysis of the primary endpoints of each of the studies and the first-ranked secondary endpoint of Study 827 (sustained clinical remission).

The Committee was asked to discuss the factors they consider in defining "clinically meaningful benefit" in this patient population; considerations included a specific magnitude of difference, steroid-sparing effect, and avoidance of colectomy. The Committee was asked if the observed treatment differences for clinical remission at Week 8, at Week 52, and at both Weeks 8 and 52, were clinically meaningful; the votes were as follows: (a) Week 8: Yes=15 votes; No=1 vote; Abstain=1 vote. (b) Week 52: Yes=16 votes; No=1 vote. (c) Both Weeks 8 and 52: Yes=10 votes; No=6 votes; Abstain=1 vote. In addition, the Committee was asked if the endpoint of clinical remission at Week 52 represents a clinically meaningful endpoint; the votes were as follows: Yes=16 votes; No=1 vote (see also Sections

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2.4 and 9). The clinical reviewer noted that his evaluation of the risk-benefit assessment for Humira was favorable based on the input of the GIDAC.

This reviewer agrees with the recommendations of the GIDAC and the clinical reviewer that the analysis of the primary endpoints of each of the studies and the first-ranked secondary endpoint of Study 827 (sustained clinical remission) demonstrate a clinically meaningful benefit.

This reviewer notes in particular that the Study 827 Week 8 clinical remission result replicates the Study 826 Week 8 clinical remission result; thus, efficacy for induction of clinical remission is demonstrated even if one concludes that the Study 826 Week 8 clinical remission result is not robust.

It should be noted further that consistent with the recommendations of the Advisory Committee, there will be a PMR for a trial to study a higher induction dose (see PMR #5 in Section 13.5) and a PMR for a trial to study trough concentrations and antibody levels at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (see PMR #6 in Section 13.5).

7.2.2 Assessment of Applicant's Response to Other Issues (Not Approvability Issues)

A summary of the Clinical/Statistical Reviewers' assessment of the Applicant's response to Items #3a, 4a, 4b, and 4c in the CR Letter is presented below; these were not approvability issues. Also, this Reviewer's assessment is included below.

Item #3a: Study 826 Secondary Endpoint Results and Subgroup Analysis by CRP

Secondary Endpoint Results of Study 826: In the initial review cycle, the statistical reviewer identified the concern about the lack of supportive evidence from the secondary endpoint results of Study 826 (i.e., first-ranked secondary endpoint was not statistically significant). The Applicant addressed the Statistical Reviewer's concern by presenting the primary and ranked secondary endpoints using the IAS-E population (the population that includes the ITT-E population of Study 826 and the ITT population of Study 827). The treatment differences in this exploratory analysis by the Applicant are all statistically significant in this pooled population (see Appendix 7 – Applicant's Analysis #3b). The statistical reviewer concluded that this is a post hoc and exploratory analysis and does not address his concern. This reviewer notes that although there was not supportive evidence from the secondary efficacy results of Study 826, there was supportive evidence from the secondary efficacy results of Study 827 (the first eight ranked secondary endpoints had statistically significant results) (see Section 7.1.2 of this CDTL Review). Thus, in this reviewer's opinion, this issue is not a concern. This reviewer further notes that this item was not deemed an approvability issue in the first review cycle.

Inconsistent Treatment Effects in Subgroup Analysis Based on CRP in Study 826: In the initial review cycle, the statistical reviewer identified the concern about inconsistent treatment effects in the subgroup analysis based on CRP (i.e., treatment difference of 13.4% in the CRP <10 mg/L subgroup, and treatment difference of -4.5% in the CRP ≥ 10 mg/L

subgroup). The Applicant addressed the Statistical Reviewer's concern by presenting the subgroup analysis based on CRP using the IAS-E population (treatment difference of 10.5% in the CRP < 10 mg/L subgroup, and treatment difference of 1.7% in the CRP ≥ 10 mg/L subgroup). The statistical reviewer concluded that this is a post hoc and exploratory analysis and does not address his concern. This reviewer notes that although there appeared to be inconsistent treatment effects in the subgroup analysis based on CRP in Study 826, this was not observed in Study 827. In Study 827, there were consistent treatment effects observed in the subgroup analysis based on CRP at Week 8 (i.e., treatment difference of 7.6% in the CRP <10 mg/L subgroup, and treatment difference of 5.1% in the CRP ≥ 10 mg/L subgroup) and at Week 52 (i.e., treatment difference of 8.7% in the CRP <10 mg/L subgroup, and treatment difference of 8.0% in the CRP ≥ 10 mg/L subgroup) (see Appendix 5 of this CDTL Review). Thus, in this reviewer's opinion, this issue is not a concern. This reviewer further notes that this item was not deemed an approvability issue in the first review cycle.

Item #4a: Study 827 Robustness of Sustained Remission Results and Missing Data

Robustness of Sustained Clinical Remission Results: In the initial review cycle, the statistical reviewer noted that the sustained clinical remission endpoint is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062). It should be noted that the original statistical analysis was based on the Cochran-Mantel-Haenszel (CMH) test. The Applicant addressed the Statistical Reviewer's concern by using the alternative methodology of logistic regression with treatment group as the factor; based on this analysis, the statistical significance remained (p=0.048). The statistical reviewer commented that it is not clear if the use of anti-TNF agents was used as a covariate in the Applicant's logistic regression analysis as detailed results were not provided. In addition, the statistical reviewer noted that the logistical regression method involves statistical models, and the fundamental assumptions for modeling methods are debatable. The secondary statistical reviewer noted that observed case and complete case sensitivity analyses were also done, and these showed a numerical trend in favor of Humira. This reviewer further notes that this item was not deemed an approvability issue in the first review cycle.

Missing Data: In the initial review cycle, the Statistical Reviewer noted that the high rates of early drop-outs (78% placebo vs. 69% adalimumab) undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug. The Applicant addressed the Statistical Reviewer's concern by noting the rules for escape (i.e., moving to open label Humira treatment). These rules were as follows:

- Partial Mayo score ≥ Baseline score on 2 consecutive visits at least 14 days apart (for subjects with a Partial Mayo score of 4 to 7 at Baseline).
- Partial Mayo score ≥ 7 on 2 consecutive visits at least 14 days apart (for subjects with a Partial Mayo score of 8 or 9 at Baseline).

The applicant noted that the higher dropout rate for placebo was due to a higher rate of open label escape in the placebo group (55% in the placebo group versus 47% in the Humira group) (see table below); the applicant noted that the higher rate of escape in the placebo group may be due to inadequate response and lack of efficacy. Thus, the applicant concluded that the elevated rate of dropout in the placebo group versus the Humira group would not undermine overall conclusions which support the overall superiority of Humira over placebo.

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The Applicant also noted that the Partial Mayo scores prior to open label escape were similar between Humira and placebo (LS Mean difference = -0.16; 95% CI: -0.46, 0.15).

Table 13. Study 827 Patient Disposition

	Placebo (n=246)	Humira (n=248)
Moved to Open Label Humira (i.e., Escape) prior to Wk 52	135 (55 %)	116 (47 %)
Discontinued during Double Blind Period	55 (22 %)	50 (20 %)
Completed to Wk 52 on Double Blind Period	56 (23%)	82 (33%)

Modified from Slide 27 of the Advisory Committee Presentation by Klaus Gottlieb. Source is Page 127 of the Applicant's Re-submission

The primary statistical reviewer continues to be concerned about the high amount of missing data and commented that with approximately 70% missing data, the results for sustained clinical remission may not be reliable. The secondary statistical reviewer noted that as pre-specified, all the subjects that moved to open-label treatment because they failed to maintain clinical response based on their partial Mayo scores (i.e., 55% in the placebo group and 47% in the Humira group) were considered treatment failures; thus, a key assumption is clinical (i.e., "Had these subjects remained in the study, they would not have been in remission at week 52."). This reviewer believes that it is not known for certain that the patients with partial Mayo scores indicating failure to maintain clinical response would fail to attain clinical remission at Week 52. However, this reviewer agrees with the Applicant's point that the higher rate of failure to maintain clinical response in the placebo group (55%) than the Humira group (47%) suggests inadequate response and lack of efficacy in the placebo group. The secondary statistical reviewer also noted that it is not clear if the bias resulting from higher drop-outs in the placebo arm would be large enough to substantially alter the observed treatment effect. This reviewer further notes that this item was not deemed an approvability issue in the first review cycle.

Item #4b: Study 827 Subgroup Analysis by Use of Azathioprine or 6-MP at Baseline

Inconsistent Treatment Effects in Subgroup Analysis By Baseline Azathioprine or 6-MP: In the initial review cycle, the statistical reviewer identified the concern about inconsistent treatment effects in the subgroup analysis for the Week 8 clinical remission endpoint in Study 827 based on baseline Azathioprine or 6-MP use (i.e., treatment difference of -2.1% in the baseline Azathioprine or 6-MP use subgroup, and treatment difference of 12.1% in the no baseline Azathioprine or 6-MP use subgroup) (see Section 7.1.4). The Applicant addressed the Statistical Reviewer's concern by presenting the subgroup analysis for the Week 8 clinical remission endpoint based on baseline Azathioprine or 6-MP use in the IAS-E population (treatment difference of 3.9% in the baseline Azathioprine or 6-MP use subgroup, and treatment difference of 10.5% in the no baseline Azathioprine or 6-MP use subgroup). The statistical reviewer concluded that this is a post hoc and exploratory analysis and does not address his concern. This reviewer notes that although there appeared to be inconsistent treatment effects for the Week 8 clinical remission endpoint in Study 827 in the subgroup analysis based on baseline Azathioprine or 6-MP use, this was observed for neither the Week 52 clinical remission endpoint in Study 827 nor the Week 8 clinical remission endpoint in Study 826. For the Week 52 endpoint in Study 827, there were consistent treatment effects observed in the subgroup analysis based on baseline Azathioprine or 6-MP use (i.e.,

treatment difference of 8.3% in the baseline Azathioprine or 6-MP use subgroup, and treatment difference of 9.0 % in the no baseline Azathioprine or 6-MP use subgroup) (see Appendix 5 of this CDTL Review). For the Week 8 endpoint in Study 826, there were consistent treatment effects observed in the subgroup analysis based on baseline Azathioprine or 6-MP use (i.e., treatment difference of 11.9% in the baseline Azathioprine or 6-MP use subgroup, and treatment difference of 7.5 % in the no baseline Azathioprine or 6-MP use subgroup) (see Appendix 4 of this CDTL Review). Thus, in this reviewer's opinion, this issue is not a concern. This reviewer further notes that this item was not deemed an approvability issue in the first review cycle.

Item #4c: Study 827 Not Designed to Demonstrate Maintenance of Clinical Remission

In the initial review cycle, the statistical reviewer identified the concern that a study design intending to show maintenance of clinical remission should re-randomize patients that achieve induction of clinical remission, and noted that the Applicant's first ranked secondary endpoint of sustained clinical remission is a measure of durability in contrast to maintenance. The Applicant addressed the statistical reviewer's concern by proposing revised indication wording of "achieving clinical remission" instead of the earlier proposal in the initial submission of "inducing and maintaining induction of clinical remission." In the current review cycle, the clinical reviewer agreed with the use of "inducing and sustaining clinical remission" to replace the Applicant's proposed wording for the indication (see Section 12 of this CDTL Review). This reviewer agrees that the proposed revised indication wording addresses this issue.

7.3 Final Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical Efficacy standpoint.

The Clinical Reviewer agreed with the Clinical Pharmacology Reviewer's recommendation for a PMR for a trial to study a higher induction dose. See PMR #5 in Section 13.5.

The Clinical Pharmacology and Clinical Reviewers agreed that there should be a PMR for a trial to address the concern of SAEs in patients receiving higher doses of Humira (because their physicians escalate the dose in response to loss of remission); the trial will evaluate trough concentrations and antibody levels at the time of loss of clinical remission and will evaluate if patients with low exposures benefit from an escalation of the dose without increasing the risk of SAEs. See PMR #6 in Section 13.5.

8. Safety

8.1 First Review Cycle

Below is summarized the safety data at the time of the initial review of the sBLA submission. More information is provided in the first cycle CDTL review by Anil Rajpal and the first cycle Clinical Review by Aisha Peterson Johnson.

Exposure: Across all three studies, the mean duration of exposure to Humira was 542.5 days (range 14 to 1,475 days). Of the 1,010 patients in the All Humira Set, 60.0% (606) used Humira for greater than 12 months, 49.6% were exposed for greater than 18 months, and 35.4% were exposed for greater than 24 months.

Deaths: There was one death reported in the three studies submitted in this Application. The patient (72902) died at age 36 on Day 543 of Humira (9 days after his last dose). He was a Caucasian male randomized to Humira 160/80/40 mg in Study 827 and continued on Humira in Study 223. During this study, the patient dose-escalated to Humira 40 every week. The patient had a non-serious event of flu syndrome, head pain, body aches, and fever 3 days prior to his death. He was found in respiratory arrest by his mother and transferred to a hospital where resuscitation efforts were unsuccessful. Autopsy revealed a bilateral adrenal hemorrhage secondary to an infectious process, the etiology of which could not be determined from the autopsy. The death was considered possibly related to study drug.

Serious Adverse Events: Serious adverse events (SAEs) are summarized below by Induction Set, Maintenance Set, and All Humira Set:

- Induction Set: During the 8 week induction periods of Studies 826 and 827, a total of 610 patients were exposed to Humira. SAEs were reported in 5 patients (3.8%) taking Humira 80/40 mg and 25 patients (5.2%) taking Humira 160/80/40 mg. In comparison, 40 patients (8.3%) in the placebo group reported an SAE. The most commonly reported

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SAEs were in the gastrointestinal disorders System Organ Class. In all treatment groups, the most commonly reported MedDRA preferred term was ulcerative colitis.

- Maintenance Set: Patients in the Maintenance Set were enrolled in Study 827 and received at least one dose of study drug between Weeks 8 and 52. Of these, 11 patients (4.9%) in the placebo group and 15 patients (6.4%) in the Humira group reported at least one SAE. Similar to the induction set, the most commonly reported SAE was ulcerative colitis.
- All Humira Set: Among all patients exposed to Humira in Studies 826, 827, and 223, a total of 223 patients (22.1%) reported at least one SAE. Similar to the induction and maintenance sets, the most commonly reported SAE was ulcerative colitis.

Common Adverse Events: Common adverse events (AEs) are summarized below by Induction Set, Maintenance Set, and All Humira Set:

- Induction Set: During the randomized, double-blind, eight-week induction period of studies 826 and 827, a total of 282 placebo patients (58.4%) and 335 Humira patients (54.9%) reported an adverse event. The most common adverse events reported by patients in any treatment group were ulcerative colitis, headache, and nasopharyngitis.
- Maintenance Set: Of patients in the Maintenance Set (i.e., received blinded treatment from Week 8 through Week 52 in Study 827), 152 (68.2%) of placebo patients and 172 (73.5%) of Humira patients reported an AE. The most commonly reported AE was ulcerative colitis. Other common AEs are in the current label.
- All Humira Set: Overall, 845 patients (83.7%) reported at least one adverse event while taking Humira. The most common AEs reported were ulcerative colitis (31.8%), nasopharyngitis (16.7%), and arthralgia (10.4%).

The Clinical Reviewer concluded that no new safety signals were identified in review of the sBLA, and that known events associated with the use of Humira appear to be adequately represented in current labeling. In addition, the Clinical Reviewer concluded that there was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies.

8.2 Current Review Cycle

For additional information, see the Current Cycle Clinical Review by Klaus Gottlieb.

The Clinical Reviewer noted that since the initial submission no new safety signals have become apparent. However, the total number of deaths has increased from 1 to 4 since the first cycle review.

No deaths were reported in Studies 826 or 827. There were 4 deaths (0.2 events/100 PYs) reported in the open-label portion of the UC clinical program through 15 April 2012. Two deaths were treatment-emergent, and 2 deaths were post-treatment (defined as greater than 70 days after last adalimumab dose). The first treatment-emergent death was described above (see Section 8.1). The second treatment-emergent death and the two post-treatment deaths are summarized below.

- Treatment-Emergent Death: A 47-year-old female had findings on autopsy that included acute pulmonary edema, general atherosclerosis including coronary arteries, hypertrophy and dilation of the right ventricle.
- Post-treatment Death: A 73-year-old female with a previous diagnosis of lymphoma (considered resolved prior to death) had an event of cardiopulmonary arrest and died 982 days after her last dose of adalimumab. No autopsy was performed.
- Post-Treatment Death: A 46-year-old female died with cause of death listed as pulmonary embolism on Day 1135, 72 days after the last dose of adalimumab. The patient suffered from morbid obesity and longstanding UC. No autopsy was performed.

The Clinical Reviewer concluded that no new safety signals were identified in review of the sBLA, and that known events associated with the use of Humira appear to be adequately represented in current labeling.

8.3 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

A PMR is recommended for a study to bank samples for future evaluation to identify genetic mutations and other biomarkers that predispose IBD patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL). See PMR #1 in Section 13.5.

A PMR is recommended for a multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics. See PMR #2 in Section 13.5.

The Clinical Reviewer agreed with the Clinical Pharmacology Reviewer's recommendation for a PMR for a trial to study a higher induction dose. See PMR #5 in Section 13.5.

The Clinical Pharmacology and Clinical Reviewers agreed that there should be a PMR for a trial to address the concern of SAEs in patients receiving higher doses of Humira (because their physicians escalate the dose in response to loss of remission); the trial will evaluate trough concentrations and antibody levels at the time of loss of clinical remission and will evaluate if patients with low exposures benefit from an escalation of the dose without increasing the risk of SAEs. See PMR #6 in Section 13.5.

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9. Advisory Committee Meeting

A meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) was convened to discuss this application on August 28, 2012.

The questions posed to the GIDAC, the results of voting, and a summary of the discussion that took place are provided below:

1. Dose Selection:

   VOTE: Based on the exposure-response data and observed treatment effect presented, has the optimal Humira dose for treatment of moderately to severely active ulcerative colitis (UC) been adequately established? Please comment on the need for further dose exploration.

   Voting Results: YES=3; NO=14; ABSTAIN=0

   Discussion: Those voting "Yes" commented that while the dose studied is clinically effective for anti-TNF naïve patients, an optimal dose has not been fully established. It was also noted that while the current dosing schedule was clinically effective in some patients, others required a higher dose of 40mg every week. The committee noted that the sponsor had requested for the product label to allow a higher dose in non responders. Such variable dosing is likely to minimize risk in responders, while allowing others to receive higher doses for clinical effectiveness. There were also comments that a post marketing dose ranging study was required.

   Those who voted "No" noted that the optimal dosing for this drug has not been fully explored given FDA's concentration response analysis. Although the dosage used demonstrated clinical efficacy, the therapeutic effect continued to rise and did not plateau for the doses studied. It was commented that a higher dose study may have facilitated a better response; hence a post approval dose response study is needed.

2. Efficacy Analysis (Studies 826 and 827):

   (a) **DISCUSSION:** Please discuss the factors that you consider in defining the term "**clinically meaningful benefit**" in patients with moderately to severely active UC.

   Voting Results: Not applicable as this is not a voting question.

   Discussion: Panel members expressed a range of opinions on this issue. Statistically significant clinical efficacy alone does not imply "clinically meaningful benefit". Such results require interpretation within the context of disease burden, safety, availability of other therapies and the therapeutic pipeline. Hence, a certain magnitude of difference between placebo and treatment groups assessed either by way of a delta or odds ratio or relative risk cannot alone determine "clinically

meaningful benefit". Safety of Humira was of particular concern to some panel members; and in particular, the long term safety of the drug had not been fully evaluated. The impact of the disease on the quality of life and the need for alternative therapies were noteworthy concerns in other opinions. The steroid sparing effects or colectomy avoiding attributes of the drug were of significant importance. Patient age, duration of disease, length of therapy, and convenience of dosing were also mentioned as factors to consider. In summary, "clinically meaningful" is a subjective measure, and apart from risk benefit analysis, is dependent on patient (and physician) preferences and their risk tolerance. Within the advisory committee there was variance in the comfort level with the risk-benefit trade off in the context of clinical effectiveness. While there was unanimity regarding the lack of long term safety record for this specific indication, given the track record of this drug for other medical conditions, most members were willing to accept the safety concerns, and endorse it despite its marginal effectiveness for UC.

(b) Clinical Remission at Week 8:
VOTE: Do the observed treatment differences (Humira 160/80/40 versus placebo) in the proportion of patients that had clinical remission at Week 8 of **9.3%** (95% CI: 0.8%, 17.9%) (Study 826) and **7.2%** (95% CI: 1.3%, 13.2%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

Voting Results: YES=15; NO=1; ABSTAIN=1

Discussion: Those voting "Yes" commented about unmet need, compliance, and convenience issues, which favored having adalimumab as a treatment option. The study did show statistical significance as compared to placebo, at week 8, albeit the differences being marginal. One member noted the long record of use of this drug and of the class of drugs. Several noted that currently given few treatment choices, adalimumab would be another option, especially for difficult to treat patients. Committee members hence endorsed Humira voting that it resulted in clinically meaningful benefit. Even the marginal benefit was acceptable given the high disease burden with regards to its impact on quality of life.

The member who voted "No" commented that although Week 8 results are statistically significant, it failed to meet the member's assessment of clinically meaningful because of inadequate information on durability of response and safety. It was also noted that the data suggest that it is best to use adalimumab as an alternative to Remicade as opposed to salvage therapy following Remicade. Data thus far suggests that benefits following Remicade are modest.

The member who voted "Abstain" commented that there wasn't enough information to provide a reliable answer and also commented that the answer could be "yes" if it could be determined that there weren't substantive safety issues, that the drug effect is durable, evidence was present to indicate adalimumab is effective in patients not adequately controlled by existing therapies, and that such data were reliable. However, the probability of "No" appeared much more likely then a "Yes," hence the abstention.

(c) Clinical Remission at Week 52:

(i) **VOTE:** Does having clinical remission at Week 52 represent a clinically meaningful endpoint? (please explain your vote)

Voting Results: YES=16; NO=1; ABSTAIN=0

Discussion: The members who voted "Yes" commented that Week 52 as a marker for durability of effect is a meaningful endpoint. It was also commented that remission is at the top of the list of what patients want to see.

The member who voted "No" commented that interpreting the question as related to the practicality of obtaining long-term data reliably, while desirable, is logistically challenging. To successfully conduct a trial of such a long duration given the likelihood of significant drop out rates and loss to follow up, without adversely impacting reliable and meaningful results is difficult.

(ii) **VOTE:** Does the observed treatment difference in the proportion of patients that had clinical remission at Week 52 of **8.8%** (95% CI: 2.9%, 14.8%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

Voting Results: YES=15; NO=1; ABSTAIN=1

Discussion: The members who voted "Yes" commented that the decision was made mainly on reasons discussed previously and due to durability of sustained response. One member noted that this is a more significant finding, showing consistency of continued exposure. Most members agreed that the result is clinically relevant at Week 52.

The member who voted "No" commented that the data does not represent clinically meaningful benefit and is not confident in the interpretation of the data at Week 52. It was also noted that the durability issue is not answered because it is a cross sectional look.

The member who voted "Abstain" noted that the decision was arrived for the same reasons as Question 2b. It was noted that the vote could be "Yes" if the agent was truly safe and if we knew the value of 8.8% was real and a vote could be "No" because we can't conclude there isn't a real risk for malignancy and serious infection.

(d) Clinical Remission at Both Weeks 8 and 52:

VOTE: Does the observed treatment difference in the proportion of patients that had clinical remission at both Weeks 8 and 52 of **4.4%** (95% CI: 0.1%, 9.0%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

Voting Results: YES=10; NO=6; ABSTAIN=1

Discussion: Members voting "Yes" commented that the magnitude of effect is disappointing, but does seem meaningful given the subset of patients who are difficult to treat. Some members expressed concerns regarding missing data for long term safety, but noted that benefits were seen.

The members who voted "No" commented that because of the unknown about safety and missing data, the answer could not be a Yes. It was also noted that the value of 4.4% for durability is very low for an agent that has the risks that are known.

One member voted "Abstain" for reasons that the magnitude of effect is disappointing but a rigorous endpoint and that the 4.4% is difficult to interpret when explaining the trial results to a patient.

3. Additional Pre-Approval Studies:

VOTE: Are there additional efficacy studies that should be conducted prior to approving Humira for moderately to severely active UC? (please explain your vote)

Voting Results: YES=3; NO=13; ABSTAIN=1

Discussion: Those who voted "Yes" commented that we need to further explore efficacy, safety, and dose. One member commented on the need for randomization trials involving patients with inadequate response or intolerance to existing therapy.

Those who voted "No" commented that there are studies needed, but not for approval of the medication and the approval should not be held up for the proposed indication. Most of these members expressed the need for post approval dosing and safety trials.

One member abstained from voting due to unclear phrasing and noted the contingency of approval should not be dependent on efficacy studies, but the medication should be tailored to specific patient populations and more studies are necessary, especially looking at the safety profile.

One member who had originally voted "Yes," subsequently noted during the explanation of the vote that she wanted to vote "No" and did not feel there is a need for additional studies before approval, but does want to see post approval studies and sub population response to adalimumab. The vote count above records her vote as "Yes".

4. Benefit-Risk Considerations:

VOTE: Do the expected benefits outweigh the known and potential risks of Humira for the treatment of patients with moderately to severely active UC based on currently available data? If YES, specify whether your answer is limited to particular population(s) defined by level of disease severity or inadequate response/intolerance to prior therapies. (please explain your vote)

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Voting Results: YES=15; NO=2; ABSTAIN=0

Discussion: Those who voted "Yes" commented that benefits outweigh the risks in various populations, given earlier discussions. The efficacy extended to patients intolerant to other anti-TNF therapies, anti-TNF naïve patients, those not responding to other conventional therapies, and populations with moderately to severely active disease. A few members noted that there is not enough data at this point to limit to certain populations.

Those who voted "No" commented that there are modest effects, but also uncertain durability and uncertain dose. One member also noted the lack of confidence in week 52 data.

5. Post-Approval Studies:

DISCUSSION: If you believe this product should be approved for moderately to severely active UC, are there any additional studies you would recommend post-approval?

Voting Results: Not applicable as this is not a voting question.

Discussion: The panel commented on the need to explore higher doses and since baseline efficacy has already been established, there is a need to maximize efficacy. It was also noted that in addition to the need for exploration of drug dosage issues, the mechanism of action of the drug needs to be looked at more in depth.

The panel also wanted to see studies which will explore when to introduce a drug of this class, who is likely to benefit, and reasons for loss of response (i.e. immunogenicity or dose related). There were comments on the need for studies in young adults/teenage population especially in terms of safety and also gender specific responses.

The need for studies evaluating the correlation of serum trough levels with clinical effectiveness was noted. Also, it was pointed out that anti-adalimumab antibody measurements were not standardized and clinically available. The sponsor commented that they were committed to developing an improved immunogenicity assay and to have it made available shortly.

10. Pediatrics

PREA does not apply to the adult indication as the pediatric indication has orphan status (designation date of May 11, 2011).[1] Thus, this sBLA was not presented to the Pediatric Research Committee (PeRC).

[1] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=340911 (accessed September 14, 2012)

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However, it should be noted that in the original sBLA submission (January 25, 2011), the Applicant requested a partial waiver for patients under the age of 6 that have been diagnosed with moderately to severely active UC, with the rationale that the number of potential patients under the age of 6 is small. The Applicant requested a deferral of studies for patients age (b) (4) diagnosed with moderately to severely active UC.

A meeting with the Applicant occurred on August 23, 2011 to discuss their pediatric plan (see meeting minutes filed under IND 100,103). Recommendations were given on the design of the study.

A PMC to conduct a pediatric study is recommended. See PMC #7 in Section 13.6.

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Adalimumab has been approved and marketed since 2002. Preclinical studies have not pointed to any problems with QT prolongation due to adalimumab, and postmarketing experience with adalimumab has not identified a concern regarding QT prolongation.

11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary by Khairy Malek, dated September 14, 2011 for complete information.

A site inspection was conducted by the Division of Scientific Investigations (DSI) of Site 29080 of Study 826 (Location: Vaughn, Ontario, Canada; Investigator: Susan Greenbloom, M.D.) This site was selected because it had the highest enrollment (approximately 10% of the patients in Study 826). No regulatory violations were observed during the inspection. DSI recommended that data from the inspected site can be used in support of the sBLA.

12. Labeling

The Applicant was requested to revise the label and medication guide. The most notable revisions are summarized below.

Physician Labeling:

- Indications and Usage (Section 1.6 of Label): Rather than the wording proposed in the initial submission (inducing and maintaining clinical remission) or in the re-submission (achieving clinical remission), the wording of "inducing and sustaining clinical remission" was used. In addition, "inadequate response to conventional therapy" was replaced with "inadequate response to immunosuppressants such as corticosteroids,

azathioprine, or 6-mercaptopurine (6-MP)" to describe the population that was studied. Further, the wording of "reducing signs and symptoms" was removed. Finally, the following statement was added: "The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers."

- Dosage and Administration (Section 1.4 of Label): The Applicant's proposed statement (b) (4) was replaced with a statement to only continue Humira in patients that have shown evidence of "remission" by eight weeks. In addition, the Applicant's proposed statement (b) (4).

- Clinical Studies (Section 14.6): (b) (4) (b) (4). The table showed results for clinical remission at Week 8 and clinical remission at both Weeks 8 and 52. A paragraph describing the results in the subgroup of patients with prior TNFα-antagonist use was added.

Medication Guide:

- What is HUMIRA?: New wording (from the DMPP Reviewer) was added to match Section 1.6 of the Physician Labeling. The wording is as follows: "In adults, to help get moderate to severe ulcerative colitis (UC) under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if HUMIRA is effective in people who stopped responding to or could not tolerate TNF-blocker medicines."

In addition to these revisions, additional revisions were negotiated with the Applicant.

Many of the revisions made are based on recommendations from the DMEPA Label, Labeling, and Packaging Review, the DMPP Patient Labeling Review, the OPDP Label Review, and the SEALD Labeling Review. The reader is referred to each of these reviews for complete information.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All the review disciplines recommend approval.

13.2 Risk Benefit Assessment

The benefit of Humira for patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants (such as corticosteroids, azathioprine or 6-MP) has been established in clinical trials. However, the effectiveness of

Humira has not been established in patients who have lost response to or were intolerant to TNFα-antagonists; this has been addressed through labeling (a statement in the Indications and Usage section, and a summary of results for this subgroup in the Clinical Studies section). In addition, the label will address the concern about the modest treatment difference for sustained clinical remission by including a statement that Humira should only be continued in patients who have shown evidence of clinical remission by eight weeks of treatment. Based on what was found in those trials and what is known about Humira and pharmacologically related products, the risks of Humira appear to be acceptable in view of the established benefits.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

No postmarketing required pediatric studies are recommended; PREA does not apply to the adult indication as the pediatric indication has orphan status.[2]

However, a PMC to conduct a pediatric study is recommended. See PMC #7 in Section 13.6.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

PMR studies are recommended, with the following language for the Approval Letter:

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Humira (adalimumab) was approved on December 31, 2002, we have become aware of additional cases of Hepatosplenic T-cell Lymphoma (HSTCL), a rare form of malignancy, in patients with inflammatory bowel disease (IBD) receiving Humira (adalimumab). In addition, there are literature reports of an increased risk of serious adverse events in patients receiving higher doses of Humira (adalimumab), including opportunistic infections and malignancies.[3] We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

[2] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=340911 (accessed September 14, 2012)

[3] Bongartz T, et.al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17;295(19):2275-85.

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We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of HSTCL and other serious adverse events in patients receiving higher doses of adalimumab, including opportunistic infections and malignancies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #1 A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

The timetable you submitted on September 26, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	09/2019
Final Report Submission:	09/2020

PMR #2: A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Study Completion:	12/2027
Final Report Submission:	12/2029

PMR #3 Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2013

PMR #4 Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

The timetable you submitted on September 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	03/2018
Final Report Submission:	03/2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known risk of serious adverse events, including opportunistic infections and malignancies, in patients receiving higher doses of adalimumab.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR #5 Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

PMR #6 A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2018
Final Report Submission:	03/2019

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The postmarketing commitment below is recommended:

PMC #7 Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to

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severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

The timetable you submitted on September 26, 2012, states that you will conduct this trial according to the following schedule

Final Protocol Submission:	06/2013
Trial Completion:	06/2018
Final Report Submission:	12/2019

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: Mayo Score

The following table is taken from the Clinical Review (first review cycle) by Aisha Peterson Johnson:

Table 14. Mayo Score

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.

Stool frequency subscore* 0 = Normal number of stools for this subject 1 = 1-2 stools more than normal 2 = 3-4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment subscore*** 0 = Normal (subscores are 0) 1 = Mild disease (subscores are mostly 1's) 2 = Moderate disease (subscores are 1 to 2) 3 = Severe disease (subscores are 2 to 3) *** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Adapted with permission from KW Schroeder.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

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APPENDIX 2: CR Letter (November 21, 2011)

The issues in the first review cycle Complete Response (CR) Letter (November 21, 2011) are shown below.

Approvability Issues:

CLINICAL

1. Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are twofold.

   First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

   Second, we are concerned that you may not have adequately selected an appropriate adalimumab dose for your pivotal efficacy trials. We note the modest improvement in clinical remission rates reported in both trials (treatment differences relative to placebo in clinical remission at Week 8 of 9.3% and 7.2% in Studies M06-826 and M06-827, respectively), and the treatment difference relative to placebo in sustained clinical remission (at both Weeks 8 and 52) of 4.4% in Study M06-827.

   To address these concerns, we will need to seek expert advice at a future meeting of the Gastrointestinal Drugs Advisory Committee.

LABELING

2. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 60 1. 14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

3. During a recent inspection of the [redacted] (b) (4) facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Other Issues (Not Approvability Issues):

IMMUNOGENICITY

1. The immunogenicity assay was not adequate because the original and new immunogenicity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. Therefore, there is a need to develop an assay with improved drug tolerance. To address this issue, you should develop, qualify and implement an improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patient samples collected from clinical studies should be banked under appropriate storage conditions.

2. The immunogenicity profile for adalimumab has not been adequately assessed. Utilizing a validated AAA assay as described in Item #1 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay.

STATISTICAL

3. STUDY M06-826

a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP, 10.0 mg/L vs. CRP ~10.0 mg/L (13.4% vs. -4.5%).

4. STUDY M06-827

a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal

significance (4.1% vs. 8.5%, P = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1 % vs. 12.1 %.

c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

APPENDIX 3: Baseline Mayo Score

Baseline Mayo Score and Subscores for the ITT-A3 population of Study 826 and the ITT population of Study 827 are presented in the tables below.

Table 15: Baseline Mayo Score and Subscores, Studies 826 and 827

Baseline Characteristic	Study 826 (ITT-A3 Population)			Study 827 (ITT Population)	
	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Total Mayo Score (mean ± SD)	8.7 (1.6)	9.0 (1.6)	8.8 (1.6)	8.9 (1.8)	8.9 (1.5)
Subscores					
Endoscopy	2.5 (0.5)	2.5 (0.5)	2.4 (0.5)	2.5 (0.5)	2.5 (0.5)
Rectal Bleeding	1.6 (0.8)	1.7 (0.8)	1.7 (0.9)	1.7 (0.9)	1.7 (0.9)
Stool Frequency	2.4 (0.7)	2.5 (0.7)	2.5 (0.8)	2.6 (0.7)	2.5 (0.7)
Physician's Global Assessment	2.2 (0.5)	2.3 (0.6)	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)

Table above is modified from Study 826 CSR, Table 14.1_5.4.1 p 555, and Study 827 CSR Table 10 p 230

In both studies, baseline total Mayo score and Subscores appeared to be well-balanced between treatment groups.

However, the Statistical Reviewer concluded that there was a statistically significant difference among the distributions of subjects across treatment arms for Total Mayo Score at baseline in the Study 826 ITT-A3 Population (chi-square p-value 0.0044); i.e., there was a statistically significant difference in the frequencies of Total Mayo score values across the three treatment arms (see number and percentage of patients by each Total Mayo Score value in the table below).

Table 16: Total Mayo Score at Baseline (Study 826 ITT-A3 Population)

Total Mayo Score	6	7	8	9	10	11	12
Treatment Arm (n, %)							
Humira 160/80/40	15 (12%)	13 (10%)	24 (18%)	33 (25%)	25 (19%)	15 (12%)	5 (4%)
Humira 80/40	9 (7%)	10 (8%)	36 (27%)	26 (20%)	22 (17%)	17 (13%)	10 (8%)
Placebo	9 (7%)	28 (22%)	19 (15%)	27 (21%)	34 (26%)	8 (6%)	5 (4%)

Modified from First Review Cycle Statistics Review by Milton Fan, Page 22.

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APPENDIX 4: Selected Subgroup Analyses (Study 826)

Study 826: Induction of Clinical Remission (Week 8)

Table 17. Subgroup Analyses: Induction of Clinical Remission (Week 8) [Study 826]

Subgroup	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Gender			
Male	7/82 (8.5%)	13/83 (15.7%)	7.2%
Female	5/48 (10.4%)	11/47 (23.4%)	13.0%
Age			
<40	9/72 (12.5%)	16/74 (21.6%)	9.1%
40-64	3/54 (5.6%)	7/51 (13.7%)	8.1%
≥65	0/4 (0.0%)	1/5 (20.0%)	20.0%
Race			
White	10/117 (8.5%)	22/119 (18.5%)	10.0%
Non-white	2/13 (15.4%)	2/11 (18.2%)	2.8%
Weight			
< 70 kg	5/35 (14.3%)	11/45 (24.4%)	10.1%
≥70 kg	7/95 (7.4%)	13/85 (15.3%)	7.9%
CRP			
<10.0 mg/L	7/95 (7.4%)	21/101 (20.8%)	13.4%
≥10.0 mg/L	4/32 (12.5%)	2/25 (8.0%)	-4.5%
Smoker			
Ex-smoker	2/35 (5.7%)	6/37 (16.2%)	10.5%
Smoker	0/7 (0.0%)	4/12 (33.3%)	33.3%
Non-smoker	10/88 (11.4%)	14/81 (17.3%)	5.9%
Corticosteroid Use at baseline			
Yes	8/89 (9.0%)	12/71 (16.9%)	7.9%
No	4/41 (9.8%)	12/59 (20.3%)	10.5%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	2/52 (3.8%)	8/51 (15.7%)	11.9%
No	10/78 (12.8%)	16/79 (20.3%)	7.5%

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APPENDIX 5: Selected Subgroup Analyses (Study 827)

Study 827: Induction of Clinical Remission (Week 8)

Table 18. Subgroup Analyses: Induction of Clinical Remission (Week 8) [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	7.6%
Female	10/94 (10.6%)	18/106 (17.0%)	6.4%
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	10.1%
40-64	13/116 (11.2%)	17/105 (16.2%)	5.0%
≥65	2/12 (16.7%)	1/7 (14.3%)	-2.4%
Race			
White	23/234 (9.8%)	38/236 (16.1%)	6.3%
Non-white	0/12 (0.0%)	3/12 (25.0%)	25.0%
Weight			
< 70 kg	7/91 (7.7%)	16/95 (16.8%)	9.1%
≥70 kg	16/155 (10.3%)	25/153 (16.3%)	6.0%
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	10.3%
Yes	7/101 (6.9%)	9/98 (9.2%)	2.3%
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	7.6%
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	5.1%
Smoker			
Ex-smoker	7/88 (8.0%)	15/94 (16.0%)	8.0%
Smoker	2/19 (10.5%)	2/20 (10.0%)	-0.5%
Non-smoker	14/138 (10.1%)	24/134 (17.9%)	7.8%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%
Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	11.4%
No	10/106 (9.4%)	10/98 (10.2%)	0.8%

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Study 827: Clinical Remission at Week 52

Table 19. Clinical Remission at Week 52 [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	18/152 (11.8%)	23/142 (16.2%)	4.4%
Female	3/94 (3.2%)	20/106 (18.9%)	15.7%
Age			
<40	11/118 (9.3%)	27/136 (19.9%)	10.6%
40-64	9/116 (7.8%)	16/105 (15.2%)	7.4%
≥65	1/12 (8.3%)	0/7 (0.0%)	-8.3%
Race			
White	21/234 (9.0%)	38/236 (16.1%)	7.1%
Non-white	0/12 (0.0%)	5/12 (41.7%)	41.7%
Weight			
< 70 kg	5/91 (5.5%)	20/95 (21.1%)	15.6%
≥70 kg	16/155 (10.3%)	23/153 (15.0%)	4.7%
Prior Anti-TNF Treatment			
No	18/145 (12.4%)	33/150 (22.0%)	9.6%
Yes	3/101 (3.0%)	10/98 (10.2%)	7.2%
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	8.7%
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	8.0%
Smoker			
Ex-smoker	9/88 (10.2%)	12/94 (12.8%)	2.6%
Smoker	0/19 (0.0%)	5/20 (25.0%)	25.0%
Non-smoker	12/138 (8.7%)	26/134 (19.4%)	10.7%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	8/80 (10.0%)	17/93 (18.3%)	8.3%
No	13/166 (7.8%)	26/155 (16.8%)	9.0%
Corticosteroid Use at baseline			
Yes	10/140 (7.1%)	25/150 (16.7%)	9.6%
No	11/106 (10.4%)	18/98 (18.4%)	8.0%

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APPENDIX 6: Adjustment for Baseline Mayo Score (Applicant's Analyses)

Table 20: Applicant's Analysis #1a: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Quartile) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 25TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 25TH PERCENTILE (8) AND < MEDIAN (9)	(N=19)	(N=24)	
YES	4 (21.1)	5 (20.8)	
NO	15 (78.9)	19 (79.2)	
DIFFERENCE IN PROPORTION[B]		-0.2	
95% CONFIDENCE INTERVAL[C]		(-24.7, 24.3)	
>= MEDIAN (9) AND < 75TH PERCENTILE (10)	(N=27)	(N=33)	
YES	3 (11.1)	5 (15.2)	
NO	24 (88.9)	28 (84.8)	
DIFFERENCE IN PROPORTION[B]		4.0	
95% CONFIDENCE INTERVAL[C]		(-13.0, 21.1)	
>= 75TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

(Table above taken from Page 152 of the sBLA Resubmission dated March 30, 2012.)

Table 21: Applicant's Analysis #1b: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Tertile) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 33TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 33TH PERCENTILE (8) AND < 67TH PERCENTILE (10)	(N=46)	(N=57)	
YES	7 (15.2)	10 (17.5)	
NO	39 (84.8)	47 (82.5)	
DIFFERENCE IN PROPORTION[B]		2.3	
95% CONFIDENCE INTERVAL[C]		(-12.0, 16.7)	
>= 67TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

(Table above taken from Page 153 of the sBLA Resubmission dated March 30, 2012.)

Table 22: Applicant's Analysis #1c: Number and Percent of Subjects with Remission (NRI) per Mayo Score at Week 8 by Mayo Score Categories (Median) at Baseline (ITT-A3 Analysis Set)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.028*
< MEDIAN (9)	(N=56)	(N=52)	
YES	7 (12.5)	12 (23.1)	
NO	49 (87.5)	40 (76.9)	
DIFFERENCE IN PROPORTION[B]		10.6	
95% CONFIDENCE INTERVAL[C]		(-3.8, 24.9)	
>= MEDIAN (9)	(N=74)	(N=78)	
YES	5 (6.8)	12 (15.4)	
NO	69 (93.2)	66 (84.6)	
DIFFERENCE IN PROPORTION[B]		8.6	
95% CONFIDENCE INTERVAL[C]		(-1.2, 18.5)	

(Table above taken from Page 154 of the sBLA Resubmission dated March 30, 2012.)

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APPENDIX 7: Selected Supplemental and Exploratory Analyses Submitted by the Applicant in the Re-Submission

Selected analyses that the applicant provided in the re-submission are shown below. The numbering is by the review team. Applicant's Analysis #1 is shown in Section 7.2.1 of this CDTL Review. It should be noted that the discussion and presentation of Applicant's Analyses #9, #10, #11, and #12 shown below were provided by LaRee Tracy (Safety Statistics Team Leader) and Bradley McEvoy (Safety Statistics Reviewer) in preparation of the Advisory Committee Briefing Document.

Applicant's Analysis #2: Week 8 Remission Rates Across Analysis Populations

This analysis is summarized in the table below. The pre-specified analysis populations for Study 826 and Study 827 were the ITT-A3 and ITT populations, respectively. In addition to these analysis populations, the Applicant provided Week 8 Clinical Remission rates for additional analysis populations (ITT-E, previously defined; ITT-non-A3 and IAS-E, defined in the table below).

Table 23. Applicant's Analysis #2: Week 8 Remission Rates Across Analysis Populations (Study 826)

Study	Analysis Population	Placebo N	Humira 160/80/40 N	Rate (95% CI)	p-value
826	ITT-A3	130	130	**9.2** (0.9, 17.6)	0.031
826	ITT-non-A3*	92	93	**7.5** (-0.3, 15.3)	0.062
826	ITT-E	222	223	**8.5** (2.6, 14.4)	0.005
827	ITT	246	248	**7.1** (1.2, 12.9)	0.019
826, 827	IAS-E[#]	468	470	**8.1** (3.8, 12.1)	<0.001

The ITT-A3 and ITT-E populations of Study 826 were defined previously.
*The ITT-non-A3 population is defined as the population prior to Amendment 3 that received Humira or placebo.
[#]The IAS-E population (Induction and Maintenance Analysis Set) includes the ITT-E population of 826 and the ITT population of 827
(Table above is summarized from Figure on Page 47 of the March 30, 2012 sBLA Resubmission.)

The Clinical Reviewer and Statistical Reviewer concluded that the results from the additional analysis populations (i.e., ITT-non-A3, ITT-E, and IAS-E) are post hoc and do not alleviate concerns of the pre-specified analyses.

Applicant's Analysis #3: Primary and Secondary Analyses of Study 826 Using the ITT-E and IAS-E Population

The Applicant's Analysis #3 is summarized in the tables below. The Applicant provided the primary and secondary analyses of Study 826 using the ITT-E population (as opposed to the ITT-A3 population) and the IAS-E population.

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Table 24: Applicant's Analysis #3a: Primary and Secondary Analyses of Study 826 Using the ITT-E Population (Study 826)

Endpoint	Placebo N = 222 n (%)	ADA 160/80/40 N = 223 n (%)	*P* value[a]	Treatment Difference (%)
Primary				
Clinical remission per FM	16 (7.2)	35 (15.7)	0.005	8.5
Ranked Secondary				
Clinical response per FM	95 (42.8)	116 (52.0)	0.051	9.2
Mucosal healing (endoscopy subscore ≤ 1)	79 (35.6)	99 (44.4)	0.056	8.8
Rectal bleeding subscore (RBS) ≤ 1	147 (66.2)	162 (72.6)	0.140	6.4
Physician's global assessment (PGA) ≤ 1	98 (44.1)	119 (53.4)	0.050	9.2
Stool frequency subscore (SFS) ≤ 1	81 (36.5)	95 (42.6)	0.185	6.1

FM: Full Mayo Score
a. P value based on CMH test with in/not in the ITT-A3 Analysis Set as the stratification factor.
Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission.
(Table above modified from Page 48 of the sBLA Resubmission dated March 30, 2012)

Table 25: Applicant's Analysis #3b: Primary and Secondary Analyses of Studies 826 and 827 Using the IAS-E Population (Studies 826 and 827)

Endpoint	Placebo N	Placebo n (%)	ADA 160/80/40 N	ADA 160/80/40 (%)	*P* value[a]	Treatment Difference (%)
Primary						
Clinical remission per FM	468	37 (7.9)	470	75 (16.0)	< 0.001	8.1
Ranked Secondary						
Clinical response per FM	468	176 (37.6)	470	240 (51.1)	< 0.001	13.5
Mucosal healing (endoscopy subscore ≤ 1)	468	152 (32.5)	470	200 (42.6)	0.002	10.1
RBS ≤ 1	468	286 (61.1)	470	335 (71.3)	0.001	10.2
PGA ≤ 1	468	188 (40.2)	470	232 (49.4)	0.005	9.2
SFS ≤ 1	468	149 (31.8)	470	188 (40.0)	0.010	8.2

FM: Full Mayo Score
a. P value based on CMH test with 3 levels of stratification: 1) subjects in Study M06-826, 2) subjects in Study M06-827 with prior anti-TNF exposure; and 3) subjects in Study M06-827 without prior anti-TNF exposure.
Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission.
(Table above modified from Page 49 of the sBLA Resubmission dated March 30, 2012)

The Clinical Reviewer and Statistical Reviewer concluded that the results from the primary and secondary analyses in the ITT-E and IAS-E populations do not alleviate all the concerns regarding the results of the pre-specified primary analyses.

Applicant's Analysis #4: Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Applicant's Analysis #4 is summarized in the table below. The Applicant performed an analysis of the rates of Clinical Remission and Clinical Response at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8.

Table 26: Applicant's Analysis #4: Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Analysis	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value*
Original Analysis (for reference): Sustained Clinical Remission (Remission at Wks 8 and 52)	4.1% (10/246)	8.5% (21/248)	4.4%	0.047
#4a: Clinical *Remission* at Week 52 (in Week 8 Clinical Remitters)	43.5% (10/23)	51.2% (21/41)	**7.7%**	**0.618**
#4b: Clinical *Response* at Week 52 (in Week 8 Clinical Remitters)	52.2% (12/23)	63.4% (26/41)	**11.2%**	**0.400**

(Table above summarized from Pages 161-162 of the March 30, 2012 sBLA Resubmission.)

The FDA Clinical Reviewer concluded that the results of the analysis of Clinical Response and Clinical Remission at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8 are not informative and serve only as an exploratory comparison.

Applicant's Analysis #5: Clinical Response Based on Partial Mayo Score at Weeks 2, 4, and 8

To explore the timing of the onset of Humira, the Applicant explored the clinical response based on partial Mayo (PM) score at Weeks 2, 4, and 8. The analysis revealed that the treatment difference (Humira-placebo) was greatest at Week 2 and smallest at Week 4. However, the clinical response rates increased from Week 2 through Week 8 for both placebo and Humira patients. See Table 27, below.

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Table 27: Applicant's Analysis #5: Clinical Response per PM Score at Weeks 2, 4, and 8, and per FM at Week 8, Study 827

	Number (%) of Subjects			
Study Visit	Placebo N = 246	ADA N = 248	Treatment Difference[a] (%)	*P* value[b]
Week 2 PM	49 (19.9)	97 (39.1)	19.2	< 0.001
Week 4 PM	78 (31.7)	113 (45.6)	13.9	0.002
Week 8 PM	86 (35.0)	123 (49.6)	14.6	0.001
Week 8 FM	85 (39.2)	125 (55.6)	16.4	< 0.001

a. Percent difference between active treatment and placebo.

b. *P* value to compare adalimumab with placebo was based on CMH test.

Notes: According to the NRI method, all missing clinical response values were considered to be nonresponses.

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The Clinical Reviewer concluded that the analysis of PM scores for Weeks 2 through 8 may suggest that patients respond early to treatment with Humira; however, this analysis does not reveal if patients who respond at Week 2 continue to be in response at Weeks 4 and 8 or if they subsequently lose that response prior to Week 8. Further, the Clinical Reviewer concluded that no statistical inferences can be made due to the exploratory nature of these analyses.

Applicant's Analysis #6: Re-analysis from Study 827 Using Average of Last 3 days (Rather than Standard "Worst-Ranked" Methodology)

In the pre-specified Statistical Analysis Plan (SAP), full Mayo (FM) scores were calculated using worst-rank methodology (i.e. the worst subscore from the past 3 days of the patient subject diary for Stool Frequency Score (SFS) and Rectal Bleeding Score (RBS) was used to calculate the Mayo score for each visit). To evaluate the possible impact of worst score versus average score methodology in Study 827, the Applicant undertook an exploratory analysis of selected patients from sites with readily-available diary data and re-calculated FM scores using the average SFS and RBS subscores from the three days prior to each visit.

To conduct this analysis, the Applicant included patients who had completed Study 827 and were currently participating in the long-term Study 223. The Applicant included three to four patients from each of the thirteen sites who reported still having readily-available diary data of both placebo and Humira patients. In the end, data from only 16 patients was used for this analysis. The results of this exploratory analysis revealed that using the average method to calculate SFS and RBS (instead of the worst-rank method) may have resulted in Week 52 FM and PM scores that were 0.59 points lower. See Table 28, below.

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Table 28: Applicant's Analysis #6: Full Mayo (FM) and Partial Mayo (PM) Scores Using Worst-case vs. Average Scores, Study 827

	Baseline	Week 52	Δ[a]	Overall Δ[b]
FM Scores				
ADA, N = 9				
Worst score from the past 3 days	9.11	2.89	6.22	
Average score from the past 3 days	9.00	2.33	6.67	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	9.57	4.29	5.28	
Average score from the past 3 days	9.00	3.86	5.14	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**
PM Scores				
ADA, N = 9				
Worst score from the past 3 days	6.44	2.00	4.44	
Average score from the past 3 days	6.33	1.44	4.89	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	6.86	2.86	4.00	
Average score from the past 3 days	6.29	2.43	3.86	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**

a. Δ – Difference between scores at Baseline and Week 52.
b. Overall Δ – difference between Δ of the worst score and average score.

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The analysis was completed with data from only 16 of the 494 patients who participated in Study 827. The Clinical Reviewer concluded that with such a small sample size, no meaningful information can be obtained. In addition, the Clinical Reviewer concluded that these data cannot be relied upon for statistical inference given their *post-hoc* nature.

Applicant's Analysis #7: All-Cause and UC-related Hospitalizations (Pooled Across Studies 826 and 827)

In a further exploratory analysis, the Applicant presented pooled data from Studies 826 and 827 to evaluate hospitalization rates with active drug and placebo. As previously pointed out, these two studies had significant design differences that make pooling of data for efficacy analysis highly problematic. The chief concerns are that patients in Study 826 were naïve to TNF-alpha-antagonists whereas 40 % of subjects in Study 827 were anti-TNF-experienced. Moreover, a protocol change (Amendment 3) in Study 826 led to the addition of the lower dose treatment arm. The hospitalizations of these patients were not used for the Applicant's hospitalization analysis because they "did not perform significantly better than subjects

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randomized to placebo for the primary endpoint."[4] Whether this is a valid reason is arguable: (1) This is a post-hoc justification; (2) a lower dose may not translate into an improvement in the Mayo score (primary endpoint), however, it may stabilize the patient enough to prevent a hospitalization.

While the Applicant presents data from several different sensitivity analyses which support their general conclusion (patients on active drug have fewer hospitalizations), other types of sensitivity analyses are not given: For example, results broken out by individual studies (826 and 827 not pooled) would be of interest and also an analysis that keeps patients on the low dose arm in Study 826 (pre-amendment) in the analysis.

The tables below are given for the purpose of reference.

Table 29: Applicant's Analysis 7a: All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

Outcome	n/PYs at Risk[a] (%) ADA 160/80/40[b] N = 471	n/PYs at Risk[a] (%) Placebo N = 468	Relative Risk of ADA/Placebo (95% CI)	*P* value[c]
All-cause hospitalization	67/379 (18)	56/214 (26)	0.7 (0.5, 1.0)	0.030
UC-related hospitalization	45/389 (12)	47/216 (22)	0.5 (0.4, 0.8)	0.002
UC- or drug-related hospitalization	53/385 (14)	51/215 (24)	0.6 (0.4, 0.8)	0.005

a. Reflected as denominator in the columns.
b. Combined including 40 mg every other week (eow) and every week (ew).
c. P values based on Z score.
Note: The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 67 of the March 30, 2012 sBLA Resubmission.)

Table 30: Applicant's Analysis #7b: Poisson Regression Analysis of All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

Outcome	E/PYs at Risk[a] (%) ADA 160/80/40[b] N = 471	E/PYs at Risk[a] (%) Placebo N = 468	*P* value[c]
All-cause hospitalization	83/401 (21)	69/224 (31)	0.0151
UC-related hospitalization	54/401 (13)	57/224 (25)	0.0008
UC- or drug-related hospitalization	63/401 (16)	61/224 (27)	0.0023

a. Reflected as denominator in the columns.
b. Combined including 40 mg eow and ew.
c. P values based on Poisson regression with time offset.
Note: Numbers in parentheses represent the number of hospitalizations on an annualized basis. The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 68 of the March 30, 2012 sBLA Resubmission.)

[4]Adalimumab Risk of Hospitalization and Colectomy R&D/12/280 submitted with the March 30, 2012 sBLA Resubmission.

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The Clinical Reviewer concluded that the analyses are post hoc and do not alleviate concerns regarding the results of the pre-specified analyses.

An Information Request was sent to the Applicant to address the additional concerns about pooling of data across studies and the selective exclusion/inclusion of portions of the ITT population. The Applicant responded to this request and provided analyses of hospitalization data for each study and treatment arm separately; this data is summarized in the following table.

Table 31. Exploratory Analysis 7 (Response to Information Request)

Analysis Set Outcome	ADA 80/40 *P* value vs. Placebo	ADA 160/80 *P* value vs. Placebo
Study M06-826 ITT-E Safety		
Analysis Set		
All-cause hospitalization	0.117	0.046
UC-related hospitalization	0.038	0.012
Study M06-826 ITT-A3 Safety		
Analysis Set		
All-cause hospitalization	0.570	0.442
UC-related hospitalization	0.392	0.205
Study M06-827 ITT Safety Analysis		
Set		
All-cause hospitalization	n/a	0.271
UC-related hospitalization	n/a	0.060

Table above is from the Clinical Review. Source: July 24, 2012 Response to the June 19, 2012 Clinical Information Request.

The all cause hospitalizations are a more robust measure of efficacy than UC-related hospitalizations which are un-adjudicated. In the analysis of individual studies the nominal p-values no longer suggest that the risk of hospitalization is lower with Humira. The ITT-E analysis set is exploratory by itself and an exploratory look at data in this set is even more difficult to interpret.

Applicant's Analysis #8: Partial Mayo Score Before and After Dose Escalation in Study 223

Applicant's Analysis #8 is summarized in the tables below.[5] This analysis is directly related to the CR Letter concern that the appropriate adalimumab dose for the pivotal efficacy trials may not have been selected (see Section 7.1.3). It is possible that the modest clinical

[5] The analysis of dose escalation in Study 223 was submitted by the Applicant as part of the Study 223 Interim Clinical Study Report.

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remission rates observed in Studies 826 and 827 may be a reflection of an inadequate dose. (b) (4)

(b) (4)

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Study 223 allowed patients to escalate their dose from EOW to EW at Week 12 (if they entered from a blinded cohort) or at Week 2 (if they entered from an open label cohort) if they are inadequate responders or experience a disease flare (both defined based on specific partial Mayo Score and change in partial Mayo Score).

Of the total of 498 patients, 116 entered on 40 mg EW dosing from a previous study, 339 entered on 40 mg EOW dosing and did not dose escalate in Study 223, and 43 patients dose escalated from 40 mg EOW to 40 mg EW in Study 223.

Of the 43 patients that dose escalated, the number (percentage) of patients who dose escalated by week is shown in the table below:

Table 32: Number (Percentage) of Patients who Dose Escalated by Week (Study 223)

Week*	0	2	4	8	12	24	36	48	60	72	84	96
Number (%) of Patients Who Dose Escalated	0	2 (0.4%)	7 (1.4%)	8 (1.6%)	0	11 (2.2%)	5 (1.0%)	4 (0.8%)	4 (0.8%)	2 (0.4%)	0	0

*Partial Mayo Score Assessments were scheduled to occur on all these weeks.
(Table above summarized from Page 270 of the Study 223 Interim CSR dated March 13, 2012.)

Partial Mayo scores among subjects who switched from EOW dosing to EW dosing are shown in the table below.

Table 33: Partial Mayo Score Before and After Dose Escalation, As Observed (ITT-1 Analysis Set)

	Adalimumab 40 mg eow/ew, N = 498		
Measurement Time Points	n	Mean ± SD[a]	Median[a]
Last partial Mayo score on adalimumab eow	43	6.0 ± 1.93	6.0
Last partial Mayo score on adalimumab ew	39	3.3 ± 2.23	3.0
Change	39	-2.6 ± 2.45	-3.0

eow = every other week; ew = every week; ITT = intent-to-treat
a. Mean and median scores calculated based on last available Mayo score while on eow dosing and on ew dosing. Four subjects did not have a post-Baseline partial Mayo score available while on ew dosing due to the data cut-off of 31 December 2009.
Note: Summary includes only subjects who switched from eow to ew during this study.
(Table above taken from Page 119 of the Study 223 Interim Clinical Study Report dated March 13, 2012.)

The Clinical Reviewer noted that Partial Mayo scores among subjects who switched from EOW dosing to EW dosing decreased by 50% (from last EOW = 6.0 to last EW value = 3.0). However, the Clinical Reviewer concluded that these data have limited informational value regarding added efficacy of a higher dose because there was no randomization to EOW or EW, the analysis was not pre-specified, and the underlying study was open-label.

Applicant's Analysis #9: Serious Adverse Event (SAE)-Adjusted Days in Remission

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The Applicant performed an exploratory analysis adjusting the days of clinical remission for days of serious adverse events (SAEs) leading to treatment discontinuation in Study 827. In this analysis, the mean days of SAEs leading to treatment discontinuation was subtracted from days of clinical remission. Despite the mean duration of SAEs being similar between the Humira 180/60 and placebo groups (4.11 and 4.64 days, respectively), the difference in SAE-adjusted days in clinical remission was statistically significantly different between groups. This difference is driven by the large difference in days of clinical remission (85.32 vs. 52.87 days in the Humira and placebo groups, respectively; p-value < 0.001). Therefore, it is unclear what additional information the SAE-adjusted analysis of days of clinical remission provides beyond what can be inferred from the analysis that only considered days of clinical remission. Furthermore, the clinical meaningfulness of this analysis is unclear given the pooling of all SAE time without accounting for type of event and the timing of the event in relation to clinical remission, if remission occurred.

Applicant's Analysis #10: Number of Patients who Discontinued Due to Adverse Events Relative to Number of Patients in Remission at Weeks 8 and 52

The Applicant conducted an exploratory analysis of Study 827 comparing the proportion of patients who achieved clinical remission at both Weeks 8 and 52 between treatment groups relative to those that had any AE that led to treatment discontinuation. For the individual endpoints, the ADA group had more subjects in clinical remission at both Weeks 8 and 52 (21 vs. 10, ADA and placebo respectively; Fisher p-value = 0.062) and fewer patients who discontinued due to an AE (22 vs. 30, ADA and placebo respectively; Fisher p-value=0.244). From these frequencies, the Applicant estimates that for every placebo subject who achieved clinical remission at both week 8 and week 52, 3.0 placebo subjects discontinued due to AEs; for ADA, the ratio is 1.0. The clinical meaningfulness of the ratios is unclear. This approach lumps together all AEs that led to treatment discontinuation and therefore lacks in specificity of AE. This approach of lumping events can obscure imbalances between treatment groups for individual AEs.

The Applicant included a summary risk benefit measure, which is the ratio of the by-treatment risk to benefit ratios (Table 34). Specifically, the ratio of risk of discontinuing treatment due to AE to clinical remission in the placebo and ADA group is 30/10 (3.0) and 22/21 (1.0), respectively. The Applicant interprets this ratio as "placebo subjects are three times more likely to experience an AE leading to discontinuation than ADA subjects for the same level of clinical efficacy (measured by achieving clinical remission at Week 8 and Week 52)". The interpretation of this ratio of ratios is problematic for the following reasons: 1) the proportion of clinical efficacy differs between treatment groups, 2) this analysis does not fix the level of clinical efficacy in the estimation, and 3) this analysis assumes a one-to-one exchangeability for the efficacy and safety outcomes.

These same issues apply to the Applicant's risk benefit ratio obtained for subjects who discontinued treatment prematurely relative to the number of subjects in clinical remission at week 8 and clinical response at week 52 (results not presented).

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Table 34: Number of Subjects who Discontinued Due to AEs Relative to the Number of subjects in Clinical Remission at Week 8 and Week 52 During the DB Period: Adalimumab Versus Placebo (Study M06-827 ITT Analysis Set; NRI)

	Placebo N = 246	ADA N = 248	*P* value
Subjects who discontinued due to AEs	30	22	
Subjects in clinical remission at Weeks 8 and 52	10	21	
Benefit/risk ratio (95% CI)	3.0 [1.5, 6.2]	1.0 [0.6, 1.9]	0.027

(Adapted from Applicant's Table 14 in resubmission)

Applicant's Analysis #11: Net Efficacy Adjusted Risk (NEAR) Analysis

The Applicant conducted an exploratory analysis combining clinical efficacy and safety into a single estimate. Their approach redefined the efficacy endpoint by only considering subjects with the efficacy response who also did not experience a particular safety event (i.e. a specific safety event-free treatment success). The odds of experiencing a safety event-free treatment success in the ADA group were then compared to the odds in the placebo group. The Applicant referred to this analysis as the Net Efficacy Adjusted for Risk (NEAR), which is discussed in a paper by Boada and colleagues[6,7]. The Applicant interprets a NEAR OR larger than one as a benefit-risk ratio in favor of ADA compared to placebo. Using pooled data from the placebo and ADA 160/80/40 mg group from Studies 826 and 827 (IAS-E analysis set), NEAR ORs were calculated for clinical response per Full Mayo (FM) and Partial Mayo (PM) score at Week 8 for the following two safety events: serious infections, and SAEs (which included serious infections).

Beyond issues raised previously about lumping together various safety endpoints and performing a pooled analysis, the ability of this NEAR analysis to quantify benefit-risk in a clinically meaningful way is highly questionable. The limitations of this approach are threefold. First, this approach implicitly assumes that the clinical benefit of having a clinical response is of equal importance/weight as experiencing a specific safety event. Such an assumption was not justified by the Applicant and is likely inappropriate due to the varying degree of safety events considered. The implication of this one-to-one exchange of efficacy

[6] Boada JN, Boada C, García-Saíz M, et al. Net Efficacy Adjusted for Risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3580).

[7] The NEAR approach described in the publication is considered flawed. By obtaining expected counts from the marginal event counts, one is implicitly assuming that the efficacy and safety endpoints are independent. Such an assumption is incorrect and was not discussed in the source article. Further, as a consequence of their approach, if group A has a greater percentage of patients with a positive efficacy endpoint and fewer AEs compared to group B, with probability 1 the odds of treatment group A will be larger than the odds for group B (i.e., the OR>1).

In addition, the Applicant's NEAR analysis differs from the approach described in the paper by Boada et al (2008). The difference is that the Applicant uses the observed number of subject that had an AE-free treatment success, whereas the source publication uses the expected numbers based on the marginal event counts within treatment groups.

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for safety is illustrated by considering two hypothetical examples. In the first example, suppose that one ADA randomized study patient died. Using the NEAR approach, the estimated NEAR OR would differ minimally from the estimated OR from an analysis of only efficacy ignoring the potential safety concerns. In the second example, consider the week 8 remission analysis (per FM) which has 180/468 responses in the placebo group and 241/471 in the ADA group. Suppose there were 61 SAEs all occurring in the ADA group and they all occurred in patients that had a clinical response. In this case, the number of SAE-free treatment successes in the ADA group is 180/471 compared to 180/468 for placebo. In this extreme scenario (which has an alarming safety signal), per this approach and the Applicant's interpretation, the NEAR OR would be below one suggesting ADA has an unfavorable benefit-risk ratio; however, if there were 60 (or fewer) SAEs (still a large signal), the ADA group would have a favorable benefit-risk ratio. These examples suggest incongruence between the proposed quantification of benefit-risk (based on an adapted version of the NEAR) to how clinical benefit is considered along with risk.

A second limitation is that the comparison only contrasts the favorable aspects of benefit-risk, i.e. the numerator value is based on patients with clinical benefit and who did not experience the specific safety event of interest. Other aspects of benefit-risk that can be obtained from the cross-classification of the efficacy response and safety event, such as the proportion of patients that *did not* have a clinical response (e.g. no remission) but *did* have an AE that led to treatment discontinuation, are not presented in the Applicant's NEAR analysis.

A third limitation is that the comparison only considers short-term efficacy with short-term risk. The problem with this is that short-term efficacy assessment is not done without also considering long-term risk when one assesses the overall risk benefit of a product. The failure of the analysis to incorporate temporal considerations, in addition to the above points, is sufficient reason to question the results from this analysis.

Applicant's Analysis #12: Number Needed to Harm (NNH) Analysis

The number needed to harm (NNH) corresponds to the number of patients needed to treat with Humira compared to placebo to result in one adverse event (SAE, AE leading to discontinuation, serious infections and malignancies). Estimates were derived by taking the inverse of the risk difference (1/difference of proportions) based on pooled data from the UC studies or from combined data from the UC and CD studies. Several point estimates were provided by the sponsor; however, it is unclear how clinically meaningful these values are without inclusion of confidence intervals, considering estimates when including data on all Humira exposures (not just on exposure to the Humira 160/80 treatment group) and understanding the type of events included (e.g. category of AEs leading to treatment discontinuation lacks in specificity of event).

The table below provides estimates of the NNH based on combined data from the two UC studies (826 and 827) using data collected up to 52 weeks. Two estimates are provided; one based on the inverse of the difference in proportion of events between placebo and the Humira 180/60 group and the second between placebo and all Humira. In addition, 95% CI (based on asymptotic method) are included to provide a measure of variability around the NNH estimates. The proportion of all SAEs in the placebo and Humira 160/80 groups are

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10.1% and 8.3% respectively resulting NNH of -55 (1/(0.083-0.101)) with a 95% CI (-18, 53). This suggests a lower risk of SAE (when holding all other outcomes constant) in the Humira group. Also, note that the confidence intervals around several estimates presented in the table include infinity suggesting that the possibility of no difference between regimens cannot be ruled out.

Table 35: NNH Values based on Data for 0-52 Weeks (UC Studies 826 and 827 Combined)

Event	Placebo (n=483)	Humira 160/80 (n=480)	All Humira (n=1010)
All SAEs	49 (10.1)	40 (8.3)	254 (25.1)
NNH (95% CI)		*-56 (-18, 53)*	*7 (5, 9)*
AE leading to Treatment D/C	46 (9.5)	36 (7.5)	206 (20.4)
NNH (95% CI)		*-49 (-18, 65)*	*9 (7, 14)*
Serious Infections	8 (1.7)	4 (0.8)	58 (5.7)
NNH (95% CI)		*-122 (-40, 148)*	*24 (17, 47)*
Malignancy (excl. NMSC)	1 (0.2)	1 (0.2)	15 (1.5)
NNH (95% CI)		*77280 (-102, 102)*	*78 (44, 423)*

Event counts based on those reported in Sponsor's Table 26 of AC Briefing Document, NNH estimates based on inverse of the risk difference (Humira-placebo), a negative NNH suggests decreased risk in Humira group relative to placebo, a positive value suggests increased risk in Humira relative to placebo

The sponsor also provided estimates on the number needed to treat (NNT) for clinical remission, response, mucosal healing and IBDQ response. The issues raised above also apply to these analyses of NNT along with limitations in pooling data for efficacy assessments.

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/s/

ANIL K RAJPAL
09/28/2012

Table 1. Pertinent Regulatory History of Humira (BLA 125057/232)*

Date	Event
June 15, 2006	Pre-IND / Pre-Phase 3 Meeting
September 5, 2008	Advice Letter for Study 826 Statistical Analysis Plan
May 24, 2010	Advice Letter for Study 827 Statistical Analysis Plan
November 23, 2010	Pre-sBLA Meeting

*IND 100103

Key comments communicated to the sponsor during the meetings and in the advice letters included the following:

(1) Weaknesses of not having a Phase 2 program in UC: The same dose regimen (160/80/40) as that used in the Crohn's disease (CD) program might not be optimal for UC (particularly because there is no PK data to support this dose regimen in UC). Similarly, the Week 8 timepoint for assessing clinical response or clinical remission may not be the optimal choice for UC (see Pre-IND / Pre-Phase 3 Meeting Minutes).

(2) Number of Induction Studies: Usually two adequate and well-controlled studies are needed to provide substantial evidence of efficacy for an indication (see Pre-IND / Pre-Phase 3 Meeting Minutes).

(3) Design of Maintenance Study: An indication for "maintenance of clinical remission" would require that patients who are in clinical remission at Week 8 be re-randomized because without re-randomization, any effect of Humira on maintenance could be confounded with an effect on induction. As designed (without re-randomization at Week 8), the study could only support an indication of "sustained clinical remission" at Weeks 8 and 52 (see Advice Letter for Study 827 Statistical Analysis Plan).

(4) Post Hoc Analysis using Alternate Definition of Clinical Remission: Clinical remission was defined as a total Mayo score of ≤ 2 with no individual subscore >1 (see Appendix 1: Mayo Score). The Division requested the sponsor to conduct a post-hoc sensitivity analysis using the following alternate definition of clinical remission (one more in line with current Division recommendations): total Mayo score of ≤ 2 with rectal bleeding subscore=0 and endoscopy subscore=0 (see Pre-sBLA Meeting Minutes).

See the Clinical Review by Aisha Peterson Johnson for details of the Humira regulatory history.

2.2 Current Application

The application was received on January 25, 2011. It was classified as a ten-month submission with a PDUFA deadline of November 25, 2011.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon are the following:

(1) Clinical Review by Aisha Peterson Johnson, dated October 21, 2011
(2) Statistics Review by Milton Fan, dated November 1, 2011

Reference ID: 3200370

(3) Clinical Pharmacology Review by Lin Zhou, dated November 3, 2011
(4) CMC Review by Jun Park, dated October 19, 2011
(5) DSI Clinical Inspection Summary by Khairy Malek, dated September 14, 2011

The reviews should be consulted for more specific details of the current application.

3. CMC

The reader is referred to the CMC Review by Jun Park.

3.1 Issues

The CMC Reviewer noted that all quality information was submitted under the original BLA for Humira. However, the CMC Reviewer became aware during this review cycle that samples from Study M06-827 (submitted for review in the current efficacy supplement) were assayed for serum anti-adalimumab antibody (AAA) using a new immunogenicity method, while samples from Studies M02-403, M04-691 and M02-433 (studies submitted in a previous efficacy supplement for Crohn's disease) were measured for serum AAA using the original immunogenicity method approved under the original BLA.

The CMC Reviewer noted that the Clinical Pharmacology Reviewer raised a concern about the sensitivity of both AAA assays to product interference (i.e., neither the original nor the new AAA assay is able to appropriately measure AAA because of product interference) (see Section 5.1 of this CDTL Review). The CMC Reviewer concluded that an assay with improved drug tolerance should be developed.

3.2 Recommendation

The CMC Reviewer recommends the following deficiency item be communicated to the Applicant (see also Section 13.1.2 of this CDTL Review):

- The immunogenicity assay was not adequate. Develop, qualify and implement an improved validated anti-adalimumab antibody (AAA) assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patients samples collected from clinical studies should be banked under appropriate storage conditions.

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4. Nonclinical Pharmacology/Toxicology

This is a currently marketed product. No new nonclinical study data were presented in this application.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology Review by Lin Zhou.

5.1 Issues

The focus of the Clinical Pharmacology Review was on Study 827 since it was the only study in which pharmacokinetics (PK) and immunogenicity data were collected.

5.1.1 Exposure-Response Analysis

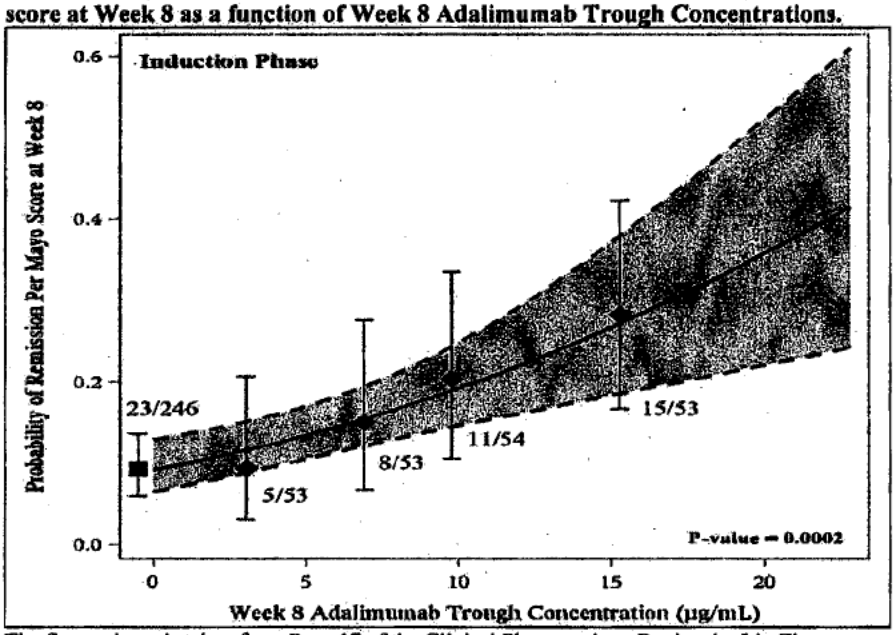
Induction Phase:

The Clinical Pharmacology Reviewer noted that the exposure-response analysis conducted based on data from Study M06-827 suggested a higher induction dose could achieve a greater treatment effect for the induction of clinical remission at Week 8. The Clinical Pharmacology Reviewer stated that this conclusion is mainly based on two observations:

(1) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression. The figure below demonstrates the exposure-response relationship for clinical remission at Week 8 suggesting that higher exposures may be associated with a higher clinical remission rate. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Multivariate logistic regression was performed to determine if the relationship between Week 8 adalimumab trough concentration and Week 8 clinical remission was confounded by baseline Mayo score and prior anti-TNF exposure. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant (p=0.0003).

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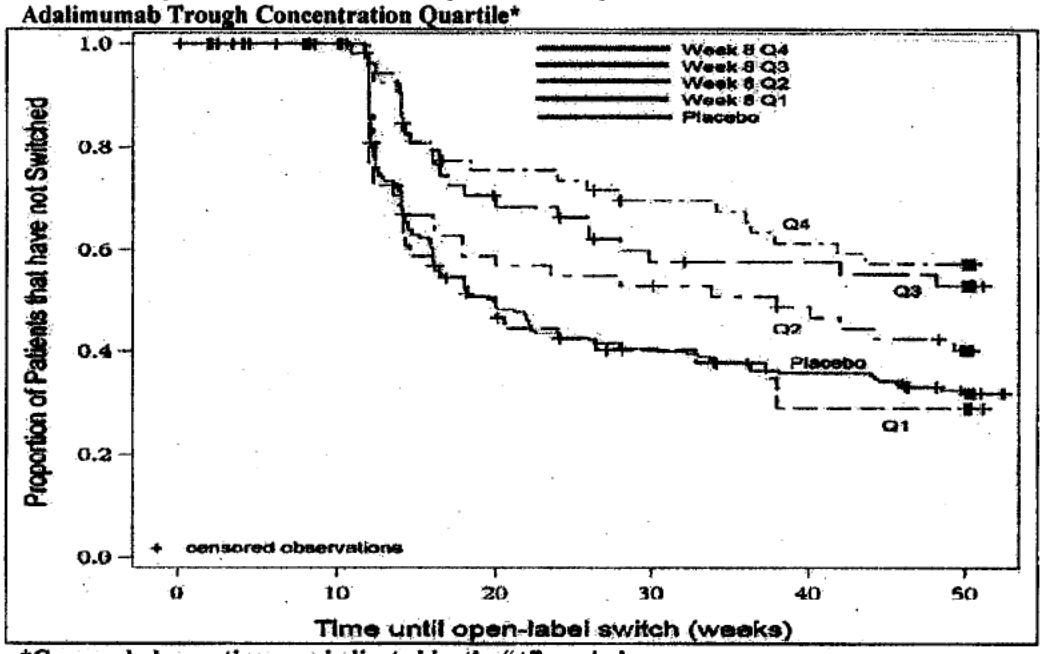
Figure 1. Logistic Regression Model of the Probability of Remission per Mayo score at Week 8 as a function of Week 8 Adalimumab Trough Concentrations.



The figure above is taken from Page 17 of the Clinical Pharmacology Review by Lin Zhou.

(2) Patients with lower exposures in the induction phase were unable to maintain response and switched to open-label treatment earlier than patients with higher exposures. The figure below demonstrates that subjects who had lower Week 8 adalimumab trough concentrations lost response earlier than the subjects with higher Week 8 concentrations. This provides additional evidence that exposures achieved by the 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that Week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy at baseline and baseline Mayo score.

Figure 2. Kaplan-Meier Plot of the Proportion of Subjects who have Not Switched vs. Week 8 Adalimumab Trough Concentration Quartile*



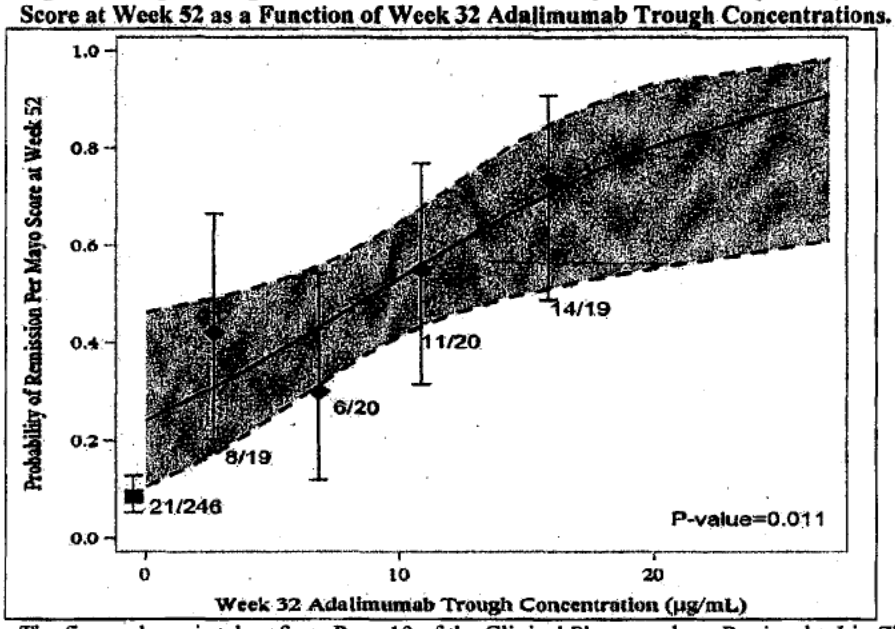
***Censored observations are indicated by the "+" symbol.**
The figure above is taken from Page 18 of the Clinical Pharmacology Review by Lin Zhou.

Maintenance Phase:

The Clinical Pharmacology Reviewer concluded that a robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Although the model relating steady state adalimumab trough concentrations to Week 52 remission demonstrates a weak trend in exposure-response (p=0.01, see figure below), suggesting a higher dose may provide additional benefit, the analysis is based on only 78 patients (31% of the total treatment population) who remained in the double-blind phase throughout the trial and had PK data. Other limitations noted by the Clinical Pharmacology Reviewer included the following: (a) The analysis dataset included non-remitters at Week 8. (b) Only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline Mayo score and prior anti-TNF use. (c) The data used in this analysis may not be representative of the actual treatment population since the clinical remission rate is 33% (43/132) for patients who remained in the double-blind treatment phase compared to 50% (39/78) for subjects who remained in double blind phase and had PK data.

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Figure 3. Logistic Regression Model of the Probability of Remission per Mayo Score at Week 52 as a Function of Week 32 Adalimumab Trough Concentrations.



The figure above is taken from Page 19 of the Clinical Pharmacology Review by Lin Zhou.

5.1.2 Immunogenicity

The Clinical Pharmacology Reviewer stated that no conclusions could be drawn regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only a small proportion of subjects had confirmed antibody status. The assessment of immunogenicity incidence was not adequate in the current submission. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration ($\geq$ 2 mcg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients.

The Clinical Pharmacology Reviewer concluded that an assay with improved drug tolerance should be developed (see Section 3.1 of this CDTL Review) and/or post dose AAA samples should be collected at time points when the adalimumab concentrations would not be expected to interfere with the immunogenicity assay (i.e., adalimumab concentration $\leq$ 2 µg/mL).

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5.2 Recommendation

The Clinical Pharmacology Reviewer recommends the following deficiency item be communicated to the Applicant (see also Section 13.1.3 of this CDTL Review):

- In order to obtain an adequate adalimumab immunogenicity profile, we recommend that you:
  (a) develop an assay with improved drug tolerance to allow detection of anti-adalimumab antibodies in the presence of adalimumab concentrations in the study samples collected from patients during treatment: and/or
  (b) collect post-dose samples at time points when the adalimumab concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL).

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because Humira is not an antimicrobial agent.

7. Clinical/Statistical - Efficacy

7.1 Issues

The reader is referred to the Clinical Review by Aisha Peterson Johnson dated October 21, 2011, and the Statistics Review by Milton Fan dated November 1, 2011 for complete information.

7.1.1 Overview of Phase 3 Clinical Trials

Studies 826 and 827 were randomized, double-blind, placebo-controlled trials submitted in support of the proposed induction and maintenance indications.

Entry Criteria:

Key entry criteria for each of the studies (826 and 827) were a total Mayo score of 6-12 and an endoscopy subscore of 2-3 despite concurrent treatment with oral corticosteroids and/or immunosuppressants. (The full listing of entry criteria for the two studies is provided in Appendix 2.)

A key difference between the two studies was the following:
- Study 826 excluded patients that previously used an anti-TNF agent whereas
- Study 827 allowed entry of patients that previously used an ant-TNF agent provided they discontinued its use due to a loss of response or intolerance to the agent. (Definitions of

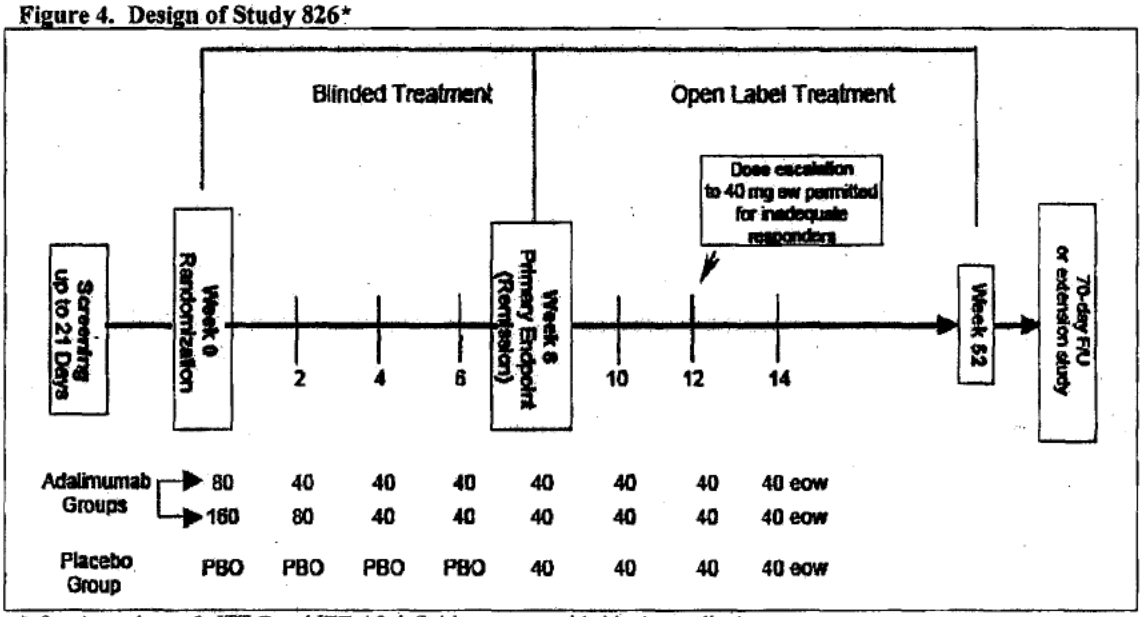
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Loss of Response and Intolerance to an Anti-TNF Agent for Study 827 are provided in Appendix 3.)

Study Design:

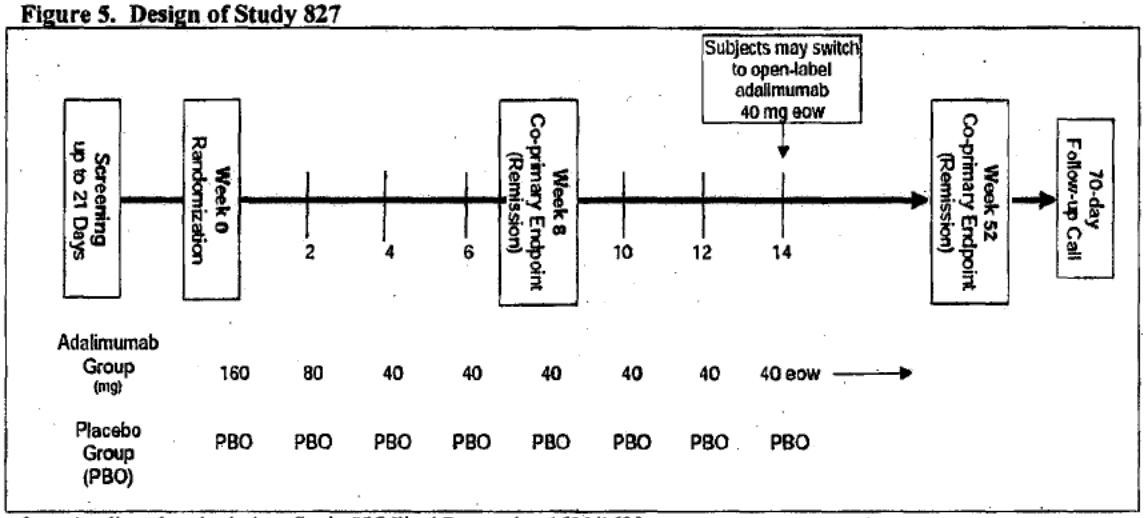
The designs of Studies 826 and 827 are summarized in the figures below and in Table 2.

Figure 4. Design of Study 826*



*after Amendment 3; ITT-E and ITT-A3 definitions are provided in Appendix 4.
from Applicant's submission, Study 826 Protocol Amendment 3, p 608/1444

Figure 5. Design of Study 827



from Applicant's submission, Study 827 Final Protocol p. 1330/1630

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Endpoints:

The endpoints are summarized below. In both studies, clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.

- Study 826: The primary efficacy endpoint of Study 826 was the proportion of subjects in clinical remission at Week 8; in addition, Study 826 included a number of ranked secondary endpoints assessed at Week 8.
- Study 827: Study 827 had a ranked co-primary efficacy endpoint (the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52). In addition, Study 827 included a number of ranked secondary endpoints assessed at Weeks 8 and/or 52 (the first-ranked secondary endpoint was the proportion of subjects in clinical remission at both Weeks 8 and 52).

(The full listing of secondary endpoints for the two studies is provided in Appendix 5.)

Table of Studies Submitted:

The table below summarizes the clinical trials submitted in support of the current application. Note that in addition to Studies 826 and 827, there was a long-term single-arm, open-label trial (Study 223) that enrolled 498 patients.

Table 2. Table of Studies Submitted

Study	Primary Endpoint	Treatment Arms	Number of patients enrolled ITT-E (ITT-A3)
826	Clinical Remission at Week 8	160/80/40* 80/40# Placebo	223 (130) 130 (130) 223 (130)
827	Co-Primary Endpoint: ▪ Clinical Remission at Week 8 ▪ Clinical Remission at Week 52	160/80/40* Placebo	258 260
223	Long-term safety and tolerability	40 mg†	498

*Adalimumab 160/80/40 SC EOW: 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and every other week
#Adalimumab 80/40 SC EOW: 80 mg at Week 0, 40 mg at Week 2 and every other week
†Adalimumab 40 mg SC EOW/EW: every other week or every week
For Study 826, the number of patients enrolled is shown as ITT-E (ITT-A3); the definitions of ITT-E and ITT-A3 are provided in Appendix 4.

7.1.2 Demographics

Baseline demographic characteristics for the ITT-A3 population of Study 826 and the ITT population of Study 827 are presented in the table below.

Reference ID: 3200370

Table 3. Demographics, Studies 826 and 827

	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Sex (n,%)					
Male	82 (63.1)	78 (60.0)	83 (63.8)	152 (61.8)	142 (57.3)
Female	48 (36.9)	52 (40.0)	47 (36.2)	94 (38.2)	106 (42.7)
Age range (years) (n,%)					
< 40 years	72 (55.4)	63 (48.5)	74 (56.9)	118 (48.0)	136 (54.8)
40 to ≤ 64 years	54 (41.5)	59 (45.4)	51 (39.2)	116 (47.2)	105 (42.3)
≥ 65 years	4 (3.1)	8 (6.2)	5 (3.8)	12 (4.9)	7 (2.8)
Mean ± SD	38.9 ± 12.68	41.6 ± 13.99	38.2 ± 13.46	41.3 ± 13.22	38.6 ± 12.47
Race (n,%)					
Caucasian	117 (90.0)	119 (91.5)	119 (91.5)	234 (95.1)	236 (95.2)
Black	5 (3.8)	6 (4.6)	2 (1.5)	4 (1.6)	7 (2.8)
Hispanic	5 (3.8)	6 (4.6)	4 (3.1)	7 (2.8)	6 (2.4)
Asian	5 (3.8)	5 (3.8)	7 (5.4)	4 (1.6)	1 (0.4)
Other	3 (2.3)	0	2 (1.5)	4 (1.6)	4 (1.6)
Weight					
(mean ± SD), kg	78.7 ±17.42	76.8 ± 15.01	75.5 ± 14.20	77.1 ± 17.31	75.3 ± 17.71
Nicotine use (n,%)					
User	7 (5.4)	8 (6.2)	12 (9.2)	19 (7.8)	20 (8.1)
Ex-user	35 (26.9)	46 (35.4)	37 (28.5)	88 (35.9)	94 (37.9)
Never used	88 (67.7)	76 (58.5)	81 (62.3)	138 (56.3)	134 (54.0)
Alcohol use (n, %)					
Drinker	57 (43.8)	62 (47.7)	62 (47.7)	125 (51.0)	132 (53.2)
Ex-drinker	7 (5.4)	5 (3.8)	9 (6.9)	11 (4.5)	8 (3.2)
Non-drinker	66 (50,8)	63 (48.5)	59 (45.4)	109 (44.5)	108 (43.5)

Study 826 CSR, Table 11 p 191 and Study 827 CSR Table 8 p 226
Table above is taken from the Clinical Review by Aisha Peterson Johnson

In both studies, randomization produced demographic subgroups which were well-balanced between treatment groups.

7.1.3 Disposition

Study 826

In Study 826, there were a total of 576 patients randomized. These patients were randomized to Humira 160/80/40 mg (n=223), Humira 80/40 mg (n=130), and placebo (n=223). A total of 575 patients were included in the ITT-E set and a total of 390 patients were included in the ITT-A3 set (the pre-specified primary analysis set). (The definitions of ITT-E and ITT-A3 are provided in Appendix 4.) See the table below.

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Table 4. Patient Disposition, Study 826, ITT-A3 population

	Placebo	Humira 80/40	Humira 160/80/40	TOTAL
Randomized	130	130	130	390
Completed Study	91 (70.0)	86 (66.2)	95 (73.1)	272 (69.7)
Discontinued Early[a]	39 (30.0)	44 (33.8)	35 (26.9)	118 (30.3)
Lack of efficacy	26 (20.0)	22 (16.9)	17 (13.1)	65 (16.7)
AE/SAE	22 (16.9)	19 (14.6)	14 (10.8)	55 (14.1)
Withdrew consent	3 (2.3)	9 (6.9)	5 (3.8)	17 (4.4)
Protocol violation	1 (0.8)	1 (0.8)	3 (2.3)	5 (1.3)
Lost to follow-up	0	3 (2.3)	1 (0.8)	4 (1.0)
Other[b]	0	4 (3.1)	1 (0.8)	5 (1.3)
Discontinued prior to Week 8	9 (6.9)	12 (9.2)	9 (6.9)	30 (7.7)
AE/SAE	6 (4.6)	7 (5.4)	4 (3.1)	17 (4.4)
Withdrew consent	0	4 (3.1)	1 (0.8)	5 (1.3)
Lost to follow-up	0	2 (1.5)	0	2 (0.5)
Lack of efficacy	5 (3.8)	5 (3.8)	2 (1.5)	12 (3.1)
Protocol violation	0	0	2 (1.5)	2 (0.5)
Other[c]	0	0	1 (0.8)	1 (0.3)

Study 826, CSR pp. 181-182/3375

a. Primary reason, patients could have discontinued for more than one reason

b. Reasons recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator discretion, non-compliance, positive TB skin test, patient wanted to start a family, and total colectomy within the 70-day follow-up period

c. Patient diagnosed with CD

Table above is modified from the Clinical Review by Aisha Peterson Johnson

While 118 patients (30.3%) discontinued Study 826 prior to completion, only 30 patients (7.7%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (4.4%) and lack of efficacy (3.1%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira dosage groups prior to Week 8 and during the entire study.

Study 827

There were a total of 518 patients randomized into Study 827 at 103 global sites. Of those patients randomized, 24 patients from 3 sites were excluded from the ITT analysis set due to site non-compliance. See the table below.

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Table 5. Patient Disposition, Study 827, ITT population

	Placebo	Humira 160/80/40	TOTAL
ITT Analysis Set	246	248	518
Completed Study	131 (53.3)	164 (66.1)	309 (59.7)
Discontinued Early[a]	115 (46.7)	94 (37.9)	209 (42.3)
Lack of efficacy	70 (28.5)	63 (25.4)	133 (26.9)
AE/SAE	25 (10.2)	12 (4.8)	37 (7.5)
Withdrew consent	4 (1.6)	8 (3.2)	12 (2.4)
Protocol violation	5 (2.0)	1 (0.4)	6 (1.2)
Lost to follow-up	0	1 (0.4)	1 (0.2)
Other[b]	11 (4.5)	9 (3.6)	20 (4.0)
Discontinued prior to Week 8	36 (14.6)	23 (9.3)	59 (11.9)
AE/SAE	10 (4.1)	5 (2.0)	15 (3.0)
Withdrew consent	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0	0	0
Lack of efficacy	15 (6.1)	13 (5.2)	28 (5.7)
Protocol violation	3 (1.2)	1 (0.4)	4 (0.8)
Other[c]	6 (2.4)	3 (1.2)	9 (1.8)

Study 827 CSR p. 220, Table 5

a. Primary reason, patients could have discontinued for more than one reason

b. Reasons recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator discretion, non-compliance, positive TB skin test, patient wanted to start a family, and total colectomy within the 70-day follow-up period

c. patient diagnosed with CD

Table above is modified from the Clinical Review by Aisha Peterson Johnson

While 209 patients (42.3%) discontinued Study 827 prior to completion, only 59 patients (11.9%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (3.0%) and lack of efficacy (5.7%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira dosage groups prior to Week 8 and during the entire study.

7.1.4 Protocol Violations

Study 826

Major protocol violations are shown in the table below.

Table 6. Major Protocol Violations, ITT-E and ITT-A3 Populations

	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Total
ITT-E patients	222	130	223	575
Failed inclusion /exclusion criteria	24 (10.8%)	9 (6.9%)	11 (4.9%)	44 (7.7%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.3%)	1 (0.2%)
Wrong treatment or incorrect dose	12 (5.4%)	10 (7.7%)	14 (6.3%)	36 (6.3%)
Prohibited Concomitant medication	19 (8.6%)	13 (10.0%)	14 (6.3%)	46 (8.0%)
ITT-A3 patients	130	130	130	390
Failed inclusion /exclusion criteria	8 (6.2%)	9 (6.9%)	8 (6.2%)	25 (6.4%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.8%)	1 (0.3%)
Wrong treatment or incorrect dose	10 (7.7%)	10 (7.7%)	11 (8.5%)	31 (7.9%)
Prohibited Concomitant medication	11 (8.5%)	13 (10.0%)	8 (6.2%)	32 (8.2%)

Study 826 CSR Tables 14.1_2.3 and 2.4 pp 517-518/3375

Table above modified from the Clinical Review by Aisha Peterson Johnson.

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The proportion of patients with protocol violations was similar across the three treatment arms. The most common protocol violation was prohibited concomitant medication for both the ITT-E and ITT-A3 populations.

Study 827

Major protocol violations are shown in the table below.

Table 7. Major Protocol Violations, ITT Population

Deviation Category	Placebo N = 246	Adalimumab N = 248	Total N = 494
Inclusion/Exclusion Criteria Violation	32 (13.0)	40 (16.1)	72 (14.6)
Developed Withdrawal Criteria/Was Not Withdrawn	0	0	0
Received Wrong Treatment or Incorrect Dose	26 (10.6)	31 (12.5)	57 (11.5)
Received Excluded Concomitant Treatment	55 (22.4)	45 (18.1)	100 (20.2)

Table above is taken from Page 223 of the Study 827 Clinical Study Report

The proportion of patients with protocol violations was similar for the two treatment arms. The most common protocol violation was received excluded concomitant treatment.

7.1.5 Induction of Clinical Remission Results

The induction of clinical remission results for Studies 826 and 827 (Humira 160/80/40 arm versus placebo) are provided in the table below.

Table 8. Induction of Clinical Remission (Week 8)

Study	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p*-value
826	9.2% (12/130)	18.5% (24/130)	9.3%	0.031
827	9.3% (23/246)	16.5% (41/248)	7.2%	0.019

Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.
Study 826: Primary endpoint was clinical remission at Week-8.
Study 827: Ranked co-primary efficacy endpoint was the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52.
*Chi-squared for Study 826, CMH for Study 827

In the Humira 80/40 group, the clinical remission rate at Week 8 was 10.0% (13/130); there was no statistically significant difference in clinical remission observed between the Humira 80/40 treatment arm and the placebo arm (p=0.833).

Ranked secondary endpoint results for Studies 826 and 827 are shown in Appendix 6.

Clinical Meaningfulness of the Observed Treatment Difference – Studies 826 and 827:

The Clinical Reviewer concluded that the observed treatment difference for induction of clinical remission of less than 10% is not likely to be clinically meaningful.

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Robustness of Data - Study 826:

The Statistical Reviewer noted that although the clinical remission rate at Week 8 in the Humira 160/80/40 group was statistically higher than that in the placebo group (see Table 8 above), these conclusions are not considered robust from a statistical perspective. The Clinical Reviewer was also concerned about the robustness of the data.

Baseline Mayo Scores:

The Statistical Reviewer noted that adjusting the primary analysis for the significantly different baseline Mayo scores resulted in a treatment difference that was not statistically significant (see the table below).

Table 9. post-hoc analysis of the proportion of subjects with remission at Week 8 controlling for Mayo score at baseline

Mayo Score at baseline	Placebo Rate	Adalimumab 80/40 Rate	p-value[a]	Adalimumab 160/80/40 Rate	p-value[a]
6	2/9 (22.2%)	5/9 (55.6%)		5/15 (33.3%)	
7	1/28 (3.6%)	1/10 (10.0%)		2/13 (15.4%)	
8	4/19 (21.1%)	4/36 (11.1%)		5/24 (20.8%)	
9	3/27 (11.1%)	1/26 (3.9%)		5/33 (15.2%)	
10	2/34 (5.9%)	1/22 (4.6%)		3/25 (12.0%)	
11	0/8 (0.0%)	0/17 (0.0%)		3/15 (20.0%)	
12	0/5 (0.0%)	1/10 (10.0%)		1/5 (20.0%)	
Combined			0.9748		0.0852

[a]p-values obtained from Cochran-Mantel-Haenszel test.
Table above is taken from the Statistical Review.

Use of Exact Testing Methods:

The significance of the analysis results is sensitive to the use of exact testing methods. Using the pre-specified test of significance, Chi-squared, the calculated p-value is 0.031 (see Table 8). However, if Fisher's Exact Test (a more conservative analysis method than the Chi-squared approximation) is used, the p-value is 0.047. This value only borders on statistical significance. See the table below.

Table 10. Chi-squared and Fisher's Exact Test, Study 826 Induction

Study	Analysis Set	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value	Test of Significance
826	ITT-A3	9.2% (12/130)	18.5% (24/130)	9.3%	0.031	Chi-squared
Same as above					0.047	Fisher's Exact Test

From Statistical Review

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Effect of Classification Status Based on a Single Subject:

The significance of the analysis results is sensitive to the classification status based on a single subject. The value of Fisher's Exact Test becomes greater than 0.05 if the remission status of one patient (0.8% change) in either treatment group changes. Specifically, if the status of one Humira patient changes from remitter to non-remitter [Case 1] or one patient in the placebo group changes from non-remitter to remitter [Case 2], the value of Fisher's Exact Test changes to 0.068 and 0.075, respectively. See table below.

Table 11. Remission Rate, 0.8% Change Sensitivity Analysis

	Placebo	Humira 160/80/40 mg	Difference	p*-value
Original Data	9.2%	18.5%	9.3%	0.0471
Case 1	9.2%	17.7%	8.5%	0.0681
Case 2	10.0%	18.5%	8.5%	0.0748

Non-responder imputation (NRI) - all patients with missing remission values were considered to be non-remitters
*p-value calculated using Fisher's Exact Test

Inconsistent Treatment Effects - Study 826:

Ranked Secondary Endpoint Results:

The Statistical Reviewer noted that the first ranked secondary endpoint (clinical response per Mayo score at Week 8) did not show evidence of a treatment benefit (see the table below).

Table 12. First-Ranked Secondary Endpoint (Study 826)

	Placebo	Humira 160/80/40	p-value
Clinical Response at Wk 8	58/130 (44.6%)	71/130 (54.6%)	0.107

Table above modified from the Clinical Review.

(See all twelve ranked secondary endpoint results for Study 826 in Appendix 6.)

Subgroup Analysis based on CRP:

The Statistical Reviewer noted that inconsistent treatment effects were shown in the subgroup analysis based on CRP (see the table below).

Table 13. Subgroup Analysis Based on CRP (Study 826)

Subgroup	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
CRP <10.0 mg/L	7/95 (7.4%)	21/101 (20.8%)	13.4%
CRP ≥10.0 mg/L	4/32 (12.5%)	2/25 (8.0%)	-4.5%

The table above is modified from the Clinical Review.

(See other selected subgroup analyses in Appendix 7.)

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Inconsistent Treatment Effects - Study 827:

Subgroup Analysis based on use of Azathioprine or 6-MP:

The Statistical Reviewer noted that a subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo (see table below).

Table 14. Subgroup Analysis based on use of Azathioprine or 6-MP (Study 827)

Azathioprine or 6-MP at Baseline	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%

The table above is modified from the Clinical Review.

(See other selected subgroup analyses in Appendix 7.)

Alternate Definition of Clinical Remission - Studies 826 and 827:

Post hoc analyses using an alternate definition of clinical remission (one more in line with current Agency recommendations) are shown below.

Table 15. Clinical Remission (Week 8), Alternate Definition of Clinical Remission*

Study	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value
826	4.6% (6/130)	11.5% (15/130)	6.9%	0.067
827	4.5% (11/246)	9.3% (23/248)	4.8%	0.049

Alternate Definition of Clinical Remission: (a) total Mayo score ≤2; (b) Rectal bleeding subscore=0 (no bleeding); (c) endoscopy subscore=0 (e.g., no friability); (d) No individual subscore >1.
p-values calculated using Fisher's Exact test.
Modified from Table in Statistical Review
NRI Method used for missing data imputation

The Clinical Reviewer noted that if the criterion "no individual subscore >1" is omitted in Study 826 (the Applicant's interpretation of the Division's request in the Pre-sBLA Meeting; see Section 2.1 of this CDTL Review), the p-value for the difference between treatment groups was statistically significant (p=0.027).

The Clinical Reviewer concluded that the post hoc analysis above does not provide convincing evidence that Humira 160/80/40 is more efficacious than placebo.

7.1.6 Maintenance of Clinical Remission Results

For the "maintenance of clinical remission" indication (Applicant's proposed label language), Study 827 was the only study submitted. However, this study was not designed to measure "maintenance of remission;" instead, Study 827 was designed to evaluate "sustained clinical remission." To support a claim of "maintenance of remission," patients in clinical

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remission at Week 8 should have been re-randomized because without re-randomization, any effect of Humira on maintenance could be confounded with an effect on induction. (This point was communicated to the sponsor in a pre-submission advice letter about the statistical analysis plan of Study 827.)

Clinical Remission at Week 52 (part of the co-primary endpoint definition):

Study 827 had a ranked co-primary efficacy endpoint: the proportion of subjects in clinical remission at Week 8 (results shown in Table 2 above), followed by the proportion of subjects in clinical remission at Week 52 (see table below).

Table 16. Clinical Remission at Week 52 (part of the co-primary endpoint definition) Study 827

Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	P-value*
8.5% (21/246)	17.3% (43/248)	8.8%	0.004

Study 827: Ranked co-primary efficacy endpoint was the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52.
*CMH stratified for baseline prior anti-TNF use

Sustained Clinical Remission (Weeks 8 and 52) (first-ranked secondary endpoint):

"Sustained clinical remission" was defined as being in remission at both Weeks 8 and 52. The first-ranked secondary endpoint of Study 827 was the proportion of subjects that had "sustained clinical remission" using this definition (see results in table below), and was examined by the Clinical Reviewer as the best reflection of whether Humira had efficacy for maintenance of remission.

Table 17. Clinical Remission at Weeks 8 and 52 (first-ranked secondary endpoint) Study 827

Placebo	Humira 160/80/40 mg	Difference (Humira-Placebo)	p-value
4.1% (10/246)	8.5% (21/248)	4.4%	0.047

Study 827: first-ranked secondary endpoint of Study 827 was the proportion of subjects that had "sustained clinical remission" (defined as being in remission at both Weeks 8 and 52)
P value to compare treatment groups was based on CMH test (stratification levels: prior anti-TNF versus anti-TNF-naïve).

See other ranked secondary endpoint results in Appendix 6.

Clinical Meaningfulness of the Observed Treatment Difference:

The Clinical Reviewer concluded that the observed treatment difference for sustained clinical remission of approximately 4% is not likely to be clinically meaningful.

Robustness of Data:

The Statistical Reviewer noted that although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance in favor of adalimumab (see table above).

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The Statistical Reviewer further noted that the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both the sustained clinical remission endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

Additional Discussion:

Given the inherent design flaws of Study 827 (i.e., patients in clinical remission at Week 8 were not re-randomized) coupled with the concerns described above, the Clinical Reviewer commented that the observed treatment difference for the "sustained clinical remission" endpoint may not represent an effect of Humira on maintenance of clinical remission. The Statistical Reviewer noted that the "sustained clinical remission" endpoint reflects a measure of durability as opposed to maintenance.

7.1.7 Subgroup Analysis by Prior Anti-TNF Use (Study 827)

Study 827 allowed entry of patients with prior use of infliximab or other anti-TNF agents. The ranked co-primary endpoint evaluation used a two-sided CMH test and adjusted for prior exposure to infliximab or other anti-TNF agents.

At Week 8, a numerically higher treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use. At Week 52, a similar treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use. See the table below.

Table 18. Remission Results, by prior anti-TNF use, Study 827

	Placebo	Humira 160/80/40		p-value	Placebo	Humira 160/80/40		p-value
No prior anti-TNF	11.0% (16/145)	21.3% (32/150)	10.3%	0.017	12.4% (18/145)	22.0% (33/150)	9.6%	0.029
Prior anti-TNF	6.9% (7/101)	9.2% (9/98)	2.3%	0.559	3.0% (3/101)	10.2% (10/98)	7.2%	0.039

Information from Table 22, CSR Study 827, p254/3632

Other selected subgroup analyses (Studies 826 and 827) are shown in Appendix 7.

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7.1.8 NNT Analysis

A number needed to treat (NNT) analysis was performed for Humira. The table below shows the results of the NNT analysis for the induction of clinical remission and "maintenance of clinical remission" / "sustained clinical remission" endpoints.

Table 19. Humira: Induction (Week 8); Sustained Remission (Weeks 8 and 52) [NNT]

Indication	Study	Timepoint	NNT	95% CI
Induction of Remission	826	Week 8	10.8	(5.7, 111)
	827	Week 8	13.9	(7.6, 76.9)
Sustained Remission	827	Weeks 8 and 52	22.7	(11.5, 666.7)

Source: Statistics Review.

7.1.9 Additional Discussion: Cross-Study Comparisons with Remicade

For adult patients with moderately to severely active UC, there is currently a product on the market—Remicade (infliximab). Remicade is also a TNF-antagonist.

Although there are limitations of cross-study comparisons, the results suggest that the magnitude of the treatment effect with Humira is lower than that with Remicade.

Induction of Clinical Remission: Remicade registration trials revealed an induction (Week 8) treatment difference (Remicade-placebo) of 24% (ACT 1) and 28% (ACT 2) with the 5 mg/kg dose (approved dose for UC). This is considerably numerically higher than the treatment difference for induction observed with Humira in Studies 826 and 827, 9.3% and 7.2%, respectively (see Table 8). Remicade and Humira were studied in similar patient populations and the studies (for both products) used the same primary endpoint for induction of clinical remission (i.e., total Mayo score of ≤ 2 with no individual subscore >1 at Week 8).

"Maintenance of Clinical Remission" / "Sustained Clinical Remission": The treatment difference for the "sustained clinical remission" endpoint seen in the Remicade maintenance study (ACT 1) was 13%. This is considerably numerically higher than the treatment difference for the "sustained clinical remission" endpoint observed with Humira in Study 827, 4.4% (see Table 17). However, it should be noted that the definition of "sustained clinical remission" differed between the Remicade study (ACT 1) and the Humira study (827). The Remicade study (ACT 1) defined "sustained clinical remission" as clinical remission at Weeks 8, 30, and 54; in contrast, the Humira study (827) defined "sustained clinical remission" as clinical remission at Weeks 8 and 52. [The definition of clinical remission was the same for both the Remicade study (ACT 1) and the Humira study (827); i.e., total Mayo score of ≤ 2 with no individual subscore >1].

NNT Analysis: A number needed to treat (NNT) analysis was performed for the induction of clinical remission and "maintenance of clinical remission" / "sustained clinical remission" endpoints for Remicade. See the table below.

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Table 20. Remicade: Induction (Week 8); Sustained Remission (Weeks 8, 30, and 52) [NNT]

Indication	Study	Timepoint	NNT	95% CIs
Induction of Clinical Remission	ACT 1	Week 8	4.2	(2.9, 7.6)
	ACT 2	Week 8	3.5	(2.7, 5.3)
Sustained Clinical Remission	ACT 1	Weeks 8, 30, and 52	7.7	(4.6, 20.6)

Source: Statistics Review.

Although there are limitations of cross-study comparisons, the NNT results suggest that considerably fewer patients need to be treated with Remicade compared with Humira (see Table 19) to achieve induction of clinical remission and sustained clinical remission.

Immunogenicity: One issue associated with the use of Remicade (infliximab) is the development of anti-drug antibodies. The development of these Human Anti-Chimeric Antibodies (antibodies against infliximab) may lead to infusion reactions and/or reduced duration of efficacy. According to current Remicade labeling, the incidence of antibodies to infliximab was 10% in Crohn's disease patients and 36-51% in psoriasis patients over one year of treatment. Because Humira is humanized, it is hypothesized that there will be less development of anti-drug antibodies. According to current Humira labeling, approximately 5% of patients developed antibodies to adalimumab in adult rheumatoid arthritis studies. However, a recently published long-term cohort study of patients taking Humira reported that 28% (76/272) of patients developed anti-adalimumab antibodies over a three year period, with 67% of these occurring during the first 28 weeks of treatment.[1] Unfortunately, the assessment of immunogenicity in the current application was not adequate and therefore, whether Humira actually offers immunogenicity advantages remains unknown.

7.2 Recommendation

A Complete Response Action is the final recommendation from a Clinical standpoint.

The following clinical deficiency item should be communicated to the Applicant (see also Section 13.1.1 of this CDTL Review):

- Your submission does not provide substantial evidence to establish the efficacy of Humira for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

  To address this deficiency, we recommend that you provide additional evidence of efficacy from either: (a) comprehensive re-analyses of outcome data from the clinical trials you have already conducted with Humira; or (b) additional adequate and well-controlled trial(s).

[1]Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg, PA, Lems WF, et al Development of Antidrug Antibodies Against Adalimumab and Association with Disease Activity and Treatment Failure During Long-term Follow-up. JAMA April 13, 2011 vol 305 no 14 p1460-1468

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The Agency plans to discuss the efficacy data presented in this application at a future meeting of the Gastrointestinal Drugs Advisory Committee.

Although the following comments are not approvability issues at this time, the Statistical Reviewer requests that the Applicant respond to the following comments in their re-submission (see also Section 13.1.4 of this CDTL Review):

➢ STUDY M06-826

1. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject.

2. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP < 10.0 mg/L vs. CRP ≥10.0 mg/L (13.4% vs. -4.5%).

➢ STUDY M06-827

1. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

2. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% vs. 12.1%.

3. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability as opposed to maintenance.

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8. Safety

8.1 Issues

The reader is referred to the Clinical Review by Aisha Peterson Johnson dated October 21, 2011 for complete information.

8.1.1 Exposure

Across all three studies, the mean duration of exposure to Humira was 542.5 days (range 14 to 1,475 days). Of the 1,010 patients in the All Humira Set, 60.0% (606) used Humira for greater than 12 months, 49.6% were exposed for greater than 18 months, and 35.4% were exposed for greater than 24 months. (See the table below.)

Table 21. Extent of Exposure, All Humira Set (Months)

Months of Exposure	Humira 40 mg every week N=402	Humira 40 mg every other week N=608	All Humira N=1010
0-1	402 (100%)	608 (100%)	1010 (100%)
>1-2	402 (100%)	560 (92.1%)	962 (95.2%)
>2-12	245 (60.9%)	379 (60.5%)	606 (60.0%)
>12-24	143 (35.6%)	262 (43.1%)	405 (40.1%)
≥24-32	59 (14.7%)	138 (22.7%)	197 (19.5%)
>32-33	52 (12.9%)	121(19.9%0	173 (17.1%)
>33-36	44 (10.0)	102 (16.8)	146 (14.5)
>36-42	27 (6.7)	62 (10.2)	89 (8.8)
>46-48	2 (0.5)	6 (1.0)	8 (0.8)
>48	1 (0.2)	2 (0.3)	3 (0.3)
Mean ± SD (days)	532.2 ± 344.03	549.3 ± 396.45	542.5 ± 376.38
Median (days)	497.0	571.0	517.5
Range (days)	35-1475	14-1470	14-1475
Total number of Humira Injections			
Mean ± SD	62.1 ± 43.14	42.4 ± 28.66	50.2 ± 36.41
Median	50.0	42.5	46.0
Range	3-199	1-112	1-199

Table 5 & 6, 4-month Safety Update p 115-120/6263

8.1.2 Safety Findings

Deaths:

There was one death reported in the three studies submitted in this Application. The patient (72902) died at age 36 on Day 543 of Humira (9 days after his last dose). He was a Caucasian male randomized to Humira 160/80/40 mg in Study 827 and continued on Humira in Study 223. During this study, the patient dose-escalated to Humira 40 ew. The patient had a non-serious event of flu syndrome, head pain, body aches, and fever 3 days prior to his death. He was found in respiratory arrest by his mother and transferred to a hospital where

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resuscitation efforts were unsuccessful. Autopsy revealed a bilateral adrenal hemorrhage secondary to an infectious process whose etiology could not be determined from the autopsy. The death was considered possibly related to study drug.

Serious Adverse Events:

SAEs are summarized below by Induction Set, Maintenance Set, and All Humira Set:

- Induction Set: During the 8 week induction periods of Studies 826 and 827, a total of 610 patients were exposed to Humira. Serious adverse events (SAEs) were reported in 5 patients (3.8%) taking Humira 80/40 mg and 25 patients (5.2%) taking Humira 160/80/40 mg. In comparison, 40 patients (8.3%) in the placebo group reported an SAE. The most commonly reported SAEs were in the gastrointestinal disorders System Organ Class. In all treatment groups, the most commonly reported MedDRA preferred term was ulcerative colitis. (See table of SAE's by SOC (Induction Set) in Appendix 8.)

- Maintenance Set: Patients in the Maintenance Set were enrolled in Study 827 and received at least one dose of study drug between Weeks 8 and 52. Of these, 11 patients (4.9%) in the placebo group and 15 patients (6.4%) in the Humira group reported at least one SAE. Similar to the induction set, the most commonly reported SAE was ulcerative colitis.

- All Humira Set: Among all patients exposed to Humira during Studies 826, 827, and 223, a total of 223 patients (22.1%) reported at least one SAE. Similar to the induction and maintenance sets, the most commonly reported SAE was ulcerative colitis. (See table of SAE's by SOC (All Humira Set) in Appendix 8.)

Common Adverse Events:

Common AEs are summarized below by Induction Set, Maintenance Set, and All Humira Set:

- Induction Set: During the randomized, double-blind, eight-week induction period of studies 826 and 827, a total of 282 placebo patients (58.4%) and 335 Humira patients (54.9%) reported adverse events. The most common adverse events reported by patients in any treatment group were ulcerative colitis, headache, and nasopharyngitis. (See table of Common AE's (Induction Set) in Appendix 8.)

- Maintenance Set: Of patients in the Maintenance Set (i.e., received blinded treatment from Week 8 through Week 52 in Study 827), 152 (68.2%) of placebo patients and 172 (73.5%) of Humira patients reported an AE. The most commonly reported AE was ulcerative colitis. Other common AES are in the current label. (See table of Common AE's (Maintenance Set) in Appendix 8.)

- All Humira Set: Overall, 845 patients (83.7%) reported at least one adverse event while taking Humira. The most common AEs reported were ulcerative colitis (31.8%),

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nasopharyngitis (16.7%), and arthralgia (10.4%). (See table of Common AE's (All Humira Set) in Appendix 8.)

8.1.3 Additional Discussion

There are known serious adverse events associated with the use of Humira. These known risks include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome.

The Clinical Reviewer concluded that there was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies.

The Clinical Reviewer stated that the safety profiles of Remicade and Humira are very similar. The Clinical Reviewer noted that according to current Remicade labeling the incidence of infusion reactions was 20%; in Humira UC studies, the incidence of injection reactions was also 20%. The Clinical Reviewer further noted that the incidence of infections in Remicade-treated patients was 36%; in Humira UC studies, the incidence of infections Humira patients was 38% (maintenance set).

8.2 Recommendation

A Complete Response Action is the final recommendation from a Clinical standpoint because of the significant uncertainty about whether the magnitude of the treatment difference observed for induction of clinical remission and for sustained clinical remission represents a clinically meaningful benefit in the proposed UC population (see Section 7.1 of this CDTL Review), and because of the known risks of Humira (see Section 8.1.3 of this CDTL Review).

9. Advisory Committee Meeting

This efficacy supplement application was not presented to an Advisory Committee.

However, during the current review cycle it was determined that the efficacy data presented in this application will be discussed at a future meeting of the Gastrointestinal Drugs Advisory Committee. This will be communicated to the Applicant in the CR Letter (see Section 13.1.1 of this CDTL Review).

10. Pediatrics

PeRC:

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This sBLA was not presented to the Pediatric Research Committee (PeRC) during this review cycle because this sBLA is not recommended for Approval during this review cycle. Presentation to PeRC may occur should this sBLA receive an Approval action during a subsequent review cycle.

PREA Requirements:

The Applicant requested a partial waiver for patients under the age of 6 that have been diagnosed with moderately to severely active UC, with the rationale that the number of potential patients under the age of 6 is small.

The Applicant requested a deferral of studies for patients age (b) (4) (b) (4) diagnosed with moderately to severely active UC.

A meeting with the Applicant occurred on August 23, 2011 to discuss their pediatric plan (see meeting minutes filed under IND 100,103).

11. Other Relevant Regulatory Issues

11.1 Lack of QT Evaluation

There was no thorough QT assessment for this product and the clinical studies did not incorporate collection of ECG data. Adalimumab has been approved and marketed since 2002. Preclinical studies have not pointed to any problems with QT prolongation due to adalimumab, and postmarketing experience with adalimumab has not identified a concern regarding QT prolongation.

11.2 Division of Scientific Investigations (DSI) Audits

The reader is referred to the DSI Clinical Inspection Summary by Khairy Malek, dated September 14, 2011 for complete information.

A site inspection was conducted by the Division of Scientific Investigations (DSI) of Site 29080 of Study 826 (Location: Vaughn, Ontario, Canada; Investigator: Susan Greenbloom, M.D.) This site was selected because it had the highest enrollment (approximately 10% of the patients in Study 826). No regulatory violations were observed during the inspection. DSI recommended that data from the inspected site can be used in support of the sBLA.

12. Labeling

Given that an Approval action is not being planned for this review cycle and there were no labeling negotiations with the Applicant, considerations regarding specific labeling issues are being deferred until the application is otherwise approvable. No DDMAC comments have been provided on labeling.

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13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

The Primary Clinical Reviewer recommends a Complete Response action because of the significant uncertainty about the effectiveness of this product in the UC population that was studied. This Reviewer concurs with this recommendation. The Statistical Reviewer did not recommend a Complete Response action, but identified a number of issues that should be communicated to the Applicant.

The CMC Reviewer and Clinical Pharmacology Reviewer have identified deficiencies related to the immunogenicity assay that should be communicated to the Applicant.

13.1.1 Clinical

CLINICAL

1. Your submission does not provide substantial evidence to establish the efficacy of Humira for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

   To address this deficiency, we recommend that you provide additional evidence of efficacy from either: (a) comprehensive re-analyses of outcome data from the clinical trials you have already conducted with Humira; or (b) additional adequate and well-controlled trial(s).

   The Agency plans to discuss the efficacy data presented in this application at a future meeting of the Gastrointestinal Drugs Advisory Committee.

13.1.2 Product Quality

PRODUCT QUALITY

2. The immunogenicity assay was not adequate. To address this issue, you should develop, qualify and implement an improved validated anti-adalimumab antibody (AAA) assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated,

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patients samples collected from clinical studies should be banked under appropriate storage conditions.

13.1.3 Clinical Pharmacology

CLINICAL PHARMACOLOGY

3. In order to obtain an adequate adalimumab immunogenicity profile, we recommend that you:
   (a) develop an assay with improved drug tolerance to allow detection of anti-adalimumab antibodies in the presence of adalimumab concentrations in the study samples collected from patients during treatment (see Item #2 above); and/or
   (b) collect post-dose samples at time points when the adalimumab concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL).

13.1.4 Statistical

STATISTICAL

Although these are not approvability issues at this time, we request that you respond to the following comments in your re-submission:

STUDY M06-826

1. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject.

2. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP < 10.0 mg/L vs. CRP ≥10.0 mg/L (13.4% vs. -4.5%).

STUDY M06-827

3. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both

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this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

4. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% vs. 12.1%.

5. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability as opposed to maintenance.

13.2 Risk Benefit Assessment

There are known significant risks of Humira. These include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome.

The outstanding benefit issue is the significant uncertainty about whether the magnitude of the treatment difference observed for induction of clinical remission and for sustained clinical remission represents a clinically meaningful benefit in the proposed UC population.

The risks of Humira in the proposed UC population are not acceptable without an established benefit.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Since this sBLA is not recommended for Approval during this review cycle, recommendations for postmarketing required pediatric studies will be made should this sBLA receive an Approval action during a subsequent review cycle.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

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Since this sBLA is not recommended for Approval during this review cycle, postmarketing requirements will be planned for negotiation with the Applicant should this sBLA receive an Approval action during a subsequent review cycle.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

Since this sBLA is not recommended for Approval during this review cycle, postmarketing commitments will be planned for negotiation with the Applicant should this sBLA receive an Approval action during a subsequent review cycle.

13.7 Recommended Comments to Applicant

None.

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APPENDIX 1: Mayo Score

The following table is taken from the Clinical Review by Aisha Peterson Johnson:

Table 22. Mayo Score

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.

Stool frequency subscore* 0 = Normal number of stools for this subject 1 = 1-2 stools more than normal 2 = 3-4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment subscore*** 0 = Normal (subscores are 0) 1 = Mild disease (subscores are mostly 1's) 2 = Moderate disease (subscores are 1 to 2) 3 = Severe disease (subscores are 2 to 3) *** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Adapted with permission from KW Schroeder.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

Reference ID: 3200370

APPENDIX 2: Inclusion and Exclusion Criteria

Study 826

Inclusion Criteria:

A subject will be eligible for study participation if he/she meets all of the following:

1. Male or female ≥ 18 years of age.
2. Diagnosis of ulcerative colitis for greater than 90 days prior to Baseline.
3. Diagnosis of active ulcerative colitis confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.
4. Active ulcerative colitis with a Mayo Score of 6-12 points and endoscopic subscore of 2-3 despite concurrent treatment with oral corticosteroids and/or immunosuppressants as defined below:
   - Stable (± 5 mg) corticosteroid dose (prednisone of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline.
   - At least a 90 day course of azathioprine or 6-MP prior to Baseline, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time. Subject must be on a stable dose for at least 28 days prior to Baseline.

   Concurrent therapy will not be required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the past 5 years and in the judgment of the investigator have failed to respond to or could not tolerate their treatment.
5. Must be able to self-administer or has caregiver who can reliably administer subcutaneous injections.
6. Must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
7. Female must be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
   - Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
   - Oral or parenteral contraceptives for 90 days prior to study drug administration
   - A vasectomized partner
8. The results of the serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Baseline Visit must be negative.
9. Judged to be in generally good health by the investigator.

Exclusion Criteria:

A subject will be excluded from the study if he/she meets any of the following criteria:

1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery.
2. Received infliximab or any other anti-TNF agent in the past.

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3. Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.
4. Received cyclosporine, tacrolimus, mycophenolate mofetil, or methotrexate within 60 days prior to Baseline.
5. Received intravenous corticosteroids within 14 days prior to Screening and during the Screening Period.
6. Received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the Screening Visit and during the Screening Period.
7. Current diagnosis of fulminant colitis and/or toxic megacolon.
8. Subjects with disease limited to the rectum (ulcerative proctitis).
9. Current diagnosis of indeterminate colitis.
10. Current diagnosis and/or history of Crohn's disease.
11. Currently receiving total parenteral nutrition (TPN).
12. Discontinued use of azathioprine, or 6-MP within 28 days of Baseline.
13. Discontinued use of corticosteroid within 14 days of Baseline.
14. Subjects using aminosalicylates for less than 90 days prior to Baseline or not on a stable dose for at least 28 days prior to Baseline or discontinued use within 28 days of Baseline.
15. Subjects with positive Clostridium difficile (C. difficile) stool assay.
16. Persistent chronic or active non-UC related infections requiring treatment with intravenous (iv) antibiotics, iv antivirals, or iv antifungals within 30 days prior to Baseline or oral antibiotics, oral antivirals, or oral antifungals within 14 days prior to Baseline.
17. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix. If the Screening colonoscopy/flexible sigmoidoscopy shows evidence of dysplasia or a malignancy, subject may not be enrolled in the study.
18. History of listeria, histoplasmosis, chronic or active Hepatitis B infection, human immunodeficiency virus (HIV), immunodeficiency syndrome, central nervous system (CNS) demyelinating disease, or untreated tuberculosis (TB).
19. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study. There should be at least a 150-day period between the last dose of study drug and either conception or initiation of breast-feeding in women of childbearing potential.
20. Poorly controlled medical condition, such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accident and any other condition, which in the opinion of the investigator, would put the subject at risk by participation in the protocol.
21. Received any investigational agent within 30 days or 5 half lives prior to Baseline (whichever is longer).
22. History of clinically significant drug or alcohol abuse during the past year.
23. Subjects with known hypersensitivity to the excipients of adalimumab as stated in the label.
24. Subjects with any prior exposure to Tysabri® (natalizumab).
25. Subjects currently taking both budesonide and prednisone (or equivalent) simultaneously.

Study 827

Reference ID: 3200370

Inclusion Criteria:

A subject will be eligible for study participation if he/she meets all of the following:

1. Male or female ≥ 18 years of age.
2. Diagnosis of ulcerative colitis for greater than 90 days prior to Baseline.
3. Diagnosis of active ulcerative colitis confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.
4. Active ulcerative colitis with a Mayo Score of 6-12 points and endoscopy subscore of 2-3 despite concurrent treatment with oral corticosteroids and/or immunosuppressants as defined below:
   - Stable (± 5 mg) corticosteroid dose (prednisone ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline, or maintenance corticosteroid dose (prednisone ≥ 10 mg/day and < 20 mg/day or equivalent) for at least 40 days prior to Baseline.
   - At least a 90 day course of azathioprine or 6-MP prior to Baseline, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time. Subject must be on a stable dose for at least 28 days prior to Baseline.

   Concurrent therapy will not be required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the past 5 years and in the judgment of the investigator have failed to respond to or could not tolerate their treatment.
5. Subjects may be included if they have previously used an anti-TNF agent (except adalimumab) and discontinued its use due to a loss of response or intolerance to the agent (see Appendix 3 for Loss of Response and Intolerance definitions).
6. Must be able to self-administer or has caregiver who can reliably administer subcutaneous injections.
7. Must be able and willing to give written informed consent and to comply with the requirements of this study protocol.
8. Female subjects must be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
9. Condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
10. Oral or parenteral contraceptives for 90 days prior to study drug administration
11. A vasectomized partner
12. The results of the serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Baseline Visit must be negative.
13. Judged to be in generally good health by the investigator.

Exclusion Criteria:

A subject will be excluded from the study if he/she meets any of the following criteria:

1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery.
2. Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.

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3. Received cyclosporine, tacrolimus, mycophenolate mofetil, or methotrexate within 60 days prior to Baseline.
4. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
5. Received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the Screening Visit or during the Screening Period.
6. Current diagnosis of fulminant colitis and/or toxic megacolon.
7. Subject with disease limited to the rectum (ulcerative proctitis).
8. Current diagnosis of indeterminate colitis.
9. Current diagnosis and/or history of Crohn's disease.
10. Currently receiving total parenteral nutrition (TPN).
11. Subject using aminosalicylates for less than 90 days prior to Baseline or not on a stable dose for at least 28 days prior to Baseline or discontinued use within 28 days of Baseline.
12. Subject with positive Clostridium difficile (C. difficile) stool assay.
13. Subject who has previously used infliximab or any anti-TNF agent within 56 days of Baseline.
14. Subject who has previously used infliximab or any anti-TNF agent and has not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction.
15. Persistent chronic or active non-UC related infections requiring treatment with intravenous (iv) antibiotics, antivirals, or antifungals within 30 days prior to Baseline or oral antibiotics, antivirals, or antifungals within 14 days prior to Baseline.

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APPENDIX 3: Definitions of Loss of Response and Intolerance to an Anti-TNF Agent (in Study 827)

The following is taken from Pages 1601-1602 of the Study 827 protocol.

Subjects who have previously been exposed to an anti-TNF agent, including infliximab, must meet one of the two conditions defined below.

Loss of Response:

The investigator judges the subject to have responded to the anti-TNF agent in the past and demonstrated a loss of response by meeting one of the following criteria after the last dose (Note: a subject with prior infliximab exposure must have responded to a dose of ≥ 5 mg/kg and demonstrated loss of response ≥ 14 days after they received at least 2 subsequent and sequential doses of ≥ 5 mg/kg at an interval not exceeding 56 days)

- Experienced an overall lack of improvement
- Experienced a worsening of the following, but not inclusive, UC related signs/symptoms:
  - Stool frequency
  - Abdominal pain
  - Rectal bleeding
  - Fever
  - Weight loss

Intolerance to Anti-TNF agent:

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction is considered significant if at least one of the clinical characteristics listed below is reported by history and is documented in progress notes or other source documents.

- Acute Reactions
  An adverse reaction, whether immunologically or non-immunologically based, which occurs during or within 24 hours of administration of an anti-TNF agent that is manifested by one or more of the sign/symptoms listed below and is judged to be related to the medication.
  - Fever > 100°F
  - Chills or rigors
  - Itching
  - Rash
  - Flushing
  - Urticaria or angioedema
  - Breathing difficulties (dyspnea, chest pain or tightness, shortness of breath, wheezing, stridor)
  - Clinical hypotension (pallor, diaphoresis, faintness, syncope), or orthostatic decrease in blood pressure

- Delayed Reactions

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APPENDIX 3: Definitions of Loss of Response and Intolerance to an Anti-TNF Agent (in Study 827)

The following is taken from Pages 1601-1602 of the Study 827 protocol.

Subjects who have previously been exposed to an anti-TNF agent, including infliximab, must meet one of the two conditions defined below.

Loss of Response:

The investigator judges the subject to have responded to the anti-TNF agent in the past and demonstrated a loss of response by meeting one of the following criteria after the last dose (Note: a subject with prior infliximab exposure must have responded to a dose of ≥ 5 mg/kg and demonstrated loss of response ≥ 14 days after they received at least 2 subsequent and sequential doses of ≥ 5 mg/kg at an interval not exceeding 56 days)

- Experienced an overall lack of improvement
- Experienced a worsening of the following, but not inclusive, UC related signs/symptoms:
  - Stool frequency
  - Abdominal pain
  - Rectal bleeding
  - Fever
  - Weight loss

Intolerance to Anti-TNF agent:

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction is considered significant if at least one of the clinical characteristics listed below is reported by history and is documented in progress notes or other source documents.

- Acute Reactions
  An adverse reaction, whether immunologically or non-immunologically based, which occurs during or within 24 hours of administration of an anti-TNF agent that is manifested by one or more of the sign/symptoms listed below and is judged to be related to the medication.
  - Fever > 100°F
  - Chills or rigors
  - Itching
  - Rash
  - Flushing
  - Urticaria or angioedema
  - Breathing difficulties (dyspnea, chest pain or tightness, shortness of breath, wheezing, stridor)
  - Clinical hypotension (pallor, diaphoresis, faintness, syncope), or orthostatic decrease in blood pressure

- Delayed Reactions

Reference ID: 3200370

An adverse reaction occurring more than 24 hours and < 14 days after anti-TNF agent administration, manifested by one or more of the following signs/symptoms and is judged to be related to the medication.

- Myalgias
- Arthralgias
- Fever > 100°F
- Malaise
- Rash

Reference ID: 3200370

APPENDIX 4: ITT-E and ITT-A3 Definitions (Study 826)

The ITT-E and ITT-A3 definitions of Study 826 are shown below followed by discussion about Protocol Amendment 3 and diagrams of the study design prior to and after Amendment 3.

Population	Definition
ITT-E	All patients with confirmed UC at Baseline who were randomized at any time during the study and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo
ITT-A3	All patients with confirmed UC at Baseline who were randomized according to the revised study design described in Amendment 3 and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo

Amendment 3 was finalized 06 August 2007 (approximately 8 months after the study began). The change was introduced for the following primary reasons:

1. To change the blinded study drug period from 12 weeks to 8 weeks and add the 80/40 mg Humira induction dosing arm.
2. To revise the inclusion criteria to clarify that current therapy with either a corticosteroid or an immunosuppressant will satisfy these inclusion criteria and to simplify the interpretation of the corticosteroid dosage requirements.
3. To expand the birth control methods listed in the inclusion criteria.
4. To expand the exclusion criteria to include any prior biological therapy and not just infliximab or other anti-TNF agents.
5. To remove methotrexate as an exclusionary medication.
6. To decrease the exclusionary duration for therapy with cyclosporine, tacrolimus, or mycophenolate mofetil from 60 days to 30 days prior to Baseline.
7. To expand prohibited therapies to exclude biologic therapies including natalizumab and abatacept.
8. To add colectomy rates as a secondary efficacy variable.
9. To revise the sample size determination to reflect the inclusion of an additional adalimumab treatment arm.

The study design prior to and after Amendment 3 is shown in the figures below.

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Figure 6. Study M06-826 (prior to Amendment 3)

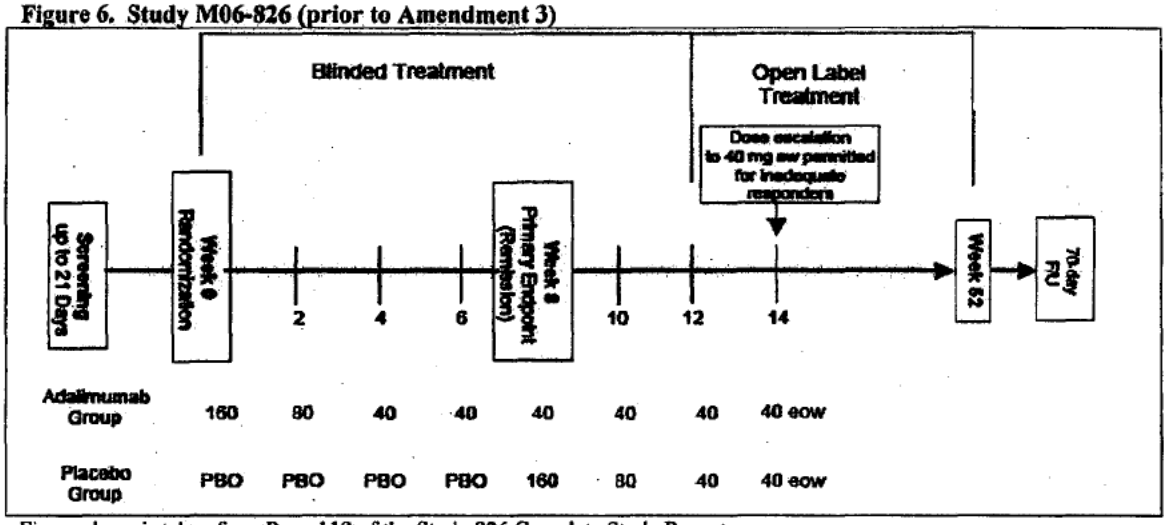


Figure above is taken from Page 119 of the Study 826 Complete Study Report.

Figure 7. Study M06-826 (after Amendment 3)

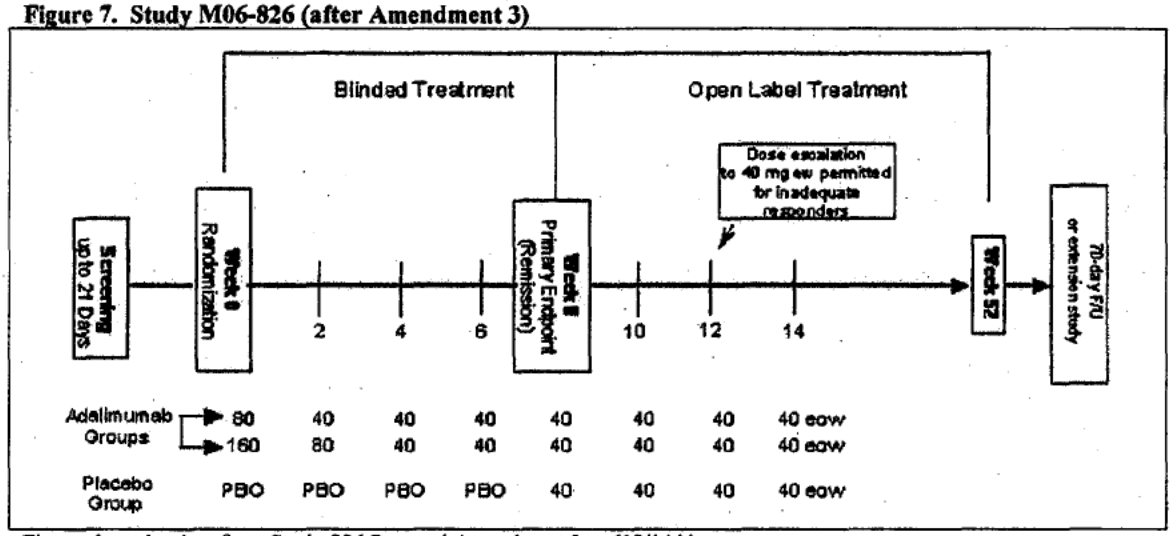


Figure above is taken from Study 826 Protocol Amendment 3, p 608/1444

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APPENDIX 5: Secondary and Other Endpoints

Study 826

Ranked secondary efficacy variables assessed at Week 8 included (in the statistical hierarchical order):

1. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 160/80/40 versus placebo).
2. Proportion of patients with mucosal healing at Week 8 (Humira 160/80/40 versus placebo).
3. Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
4. Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
5. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira160/80/40 versus placebo).
6. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 80/40 versus placebo).
7. Proportion of patients with mucosal healing at Week 8 (Humira 80/40 versus placebo).
8. Proportion of patients with rectal bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
9. Proportion of patients with Physician's Global Assessment sub-score indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (Humira 80/40 versus placebo).
10. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (Humira 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (Humira 80/40 versus placebo).

Non-ranked secondary efficacy variables:

- Proportion of patients with response per Partial Mayo Score at Weeks 2, 4, and 6.
- Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Stool Frequency sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Change from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 8.
- Change from Baseline in SF-36 at Week 8.
- Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, and 8.
- Change from Baseline in Mayo Score at Week 8.
- Time to clinical response per Partial Mayo Score (up to Week 8).

Descriptive statistics were to be presented for the OL period of the study through Week 52, including, but not limited to, the following efficacy variables:

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- Proportion of patients with remission at both Week 8 and at Week 52.
- Proportion of patients with remission at Week 52.
- Proportion of patients with response per Mayo Score at both Week 8 and Week 52.
- Time in clinical response per Partial Mayo Score.
- Proportion of patients with mucosal healing at both Week 8 and Week 52.
- Proportion of patients with mucosal healing at Week 52.
- Proportion of patients using corticosteroids at Baseline in remission at Week 8 who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids for at least 90 days and were in remission at Week 52.
- Time in steroid-free clinical response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients requiring dose escalation to 40 mg ew.
- Proportion of patients achieving response at Week 52 after dose escalation
- Proportion of patients achieving remission at Week 52 after dose escalation for a) patients who had not achieved response per Partial Mayo Score prior to dose escalation and b) patients who had achieved response per Partial Mayo Score but lost response (had inadequate response) prior to dose escalation.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding sub-score $\leq$ 1) at Week 52.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding sub-score $\leq$ 1) at both Week 8 and Week 52.
- Time in minimal rectal bleeding (Rectal Bleeding subscore $\leq$ 1).
- Proportion of patients randomized to placebo who achieve clinical response by Partial Mayo Score at Week 16.
- Proportion of patients who are IBDQ responders at Week 52.
- Change from Baseline in IBDQ at Week 52.
- Change from Baseline in SF-36 at Week 52.
- Change from Baseline in Mayo Score at Week 52.
- Change in Partial Mayo Score overtime.
- Colectomy rates during the study

<u>Study 827</u>

Ranked Secondary Variables:

1. Proportion of patients with remission (sustained) at both Weeks 8 and 52.
2. Proportion of patients who achieve response per Mayo Score at Week 8 and Week 52.
3. Proportion of patients who discontinue corticosteroid use and achieve remission at Week 52.
4. Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 52.
5. Proportion of patients with response per Mayo Score (sustained) at both Weeks 8and 52.

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6. Proportion of patients who discontinue corticosteroid use and achieve remission (sustained) at both Weeks 32 and 52.
7. Proportion of patients who are IBDQ responders at Week 52.
8. Proportion of patients who are IBDQ responders at Week 8.

Non-ranked Secondary Variables:

- Proportion of patients who achieve clinical remission at Week 32.
- Proportion of patients who achieve remission (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve clinical response at Week 32.
- Proportion of patients who achieve response per Mayo Score (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve response per Partial Mayo Score over time.
- Time to response per Partial Mayo Score.
- Time in response per Partial Mayo Score.
- Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 32.
- Proportion of patients who discontinue corticosteroid use and achieve remission at Week 32.
- Proportion of patients who have discontinued corticosteroid use at each time point after Week 8.
- Time in steroid-free response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients who are IBDQ responders at Week 32.
- Proportion of patients who are IBDQ responders (sustained) at both Weeks 8 and 52.
- Proportion of patients who are IBDQ responders (sustained) throughout Weeks 8, 32 and 52.
- Proportion of patients with IBDQ score $\geq$ 170 over time.
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score over time.
- Change from Baseline in Short Form-36 Questionnaire (SF-36) over time.
- Change from Baseline in Mayo Score over time.
- Change from Baseline in endoscopy score over time.

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APPENDIX 6: Ranked Secondary Endpoint Results

Study 826

Twelve ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint. The first ranked endpoint (clinical response per Mayo score at Week 8 in the Humira 160/80/40 mg treatment group versus placebo) had a p-value of 0.107 (statistical non-significance).

Table 23. Ranked Secondary Endpoint Results, Study 826 (ITT-A3; NRI)

	Number (%) of Subjects		
Proportion of Subjects With:[a]	**Placebo N = 130**	**Adalimumab 160/80/40 N = 130**	***P* value**[b]
1. Clinical response at Week 8	58 (44.6)	71 (54.6)	0.107
2. Mucosal healing at Week 8	54 (41.5)	61 (46.9)	0.382
3. RBS ≤ 1 at Week 8	86 (66.2)	101 (77.7)	0.038
4. PGA ≤ 1 at Week 8	61 (46.9)	78 (60.0)	0.035
5. SFS ≤ 1 at Week 8	49 (37.7)	63 (48.5)	0.080
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
6. Clinical response at Week 8	58 (44.6)	67 (51.5)	0.264
7. Mucosal healing at Week 8	54 (41.5)	49 (37.7)	0.526
8. RBS ≤ 1 at Week 8	86 (66.2)	91 (70.0)	0.506
9. PGA ≤ 1 at Week 8	61 (46.9)	70 (53.8)	0.264
10. SFS ≤ 1 at Week 8	49 (37.7)	47 (36.2)	0.797
	Placebo N = 130	**Adalimumab 160/80/40 N = 130**	
11. IBDQ response at Week 8	75 (57.7)	79 (60.8)	0.614
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
12. IBDQ response at Week 8	75 (57.7)	70 (53.8)	0.532

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore

a. Listed in rank order, as indicated by the number preceding each endpoint variable.

b. *P* value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

Copied and electronically reproduced from Applicant's Table 37, CSR, Study 826 p 223/3375

Reference ID: 3200370

Study 827

Fifteen ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint.

Table 24. Ranked Secondary Endpoints, Study 827

	Ranked Secondary Endpoint	Placebo N=249	Humira (160/80/40 mg) N=248	p-value
1	Sustained remission, Week 8 and Week 52	4.1% (10)	8.5% (21)	0.047
2	Response, Week 8	34.6% (85)	50.4% (125)	<0.001
3	Response, Week 52	18.3% (45)	30.2% (75)	0.002
4	Sustained Response, Week 8 and Week 52	12.2% (30)	23.8% (59)	<0.001
5	Mucosal healing, Week 8	31.7% (78)	41.1% (102)	0.032
6	Mucosal healing, Week 52	15.4% (38)	25.0% (62)	0.009
7	Sustained Mucosal healing, Week 8 and Week 52	10.6% (26)	18.5% (46)	0.013
8	Discontinued corticosteroid use before Week 52 and achieved remission, Wee5 52	5.7% (8)	13.3% (20)	0.035
9	PGA (physician's global assessment) ≤1, Week 8	37.4% (92)	46.0% (114)	0.058
10	SFS (stool frequency sub-score) ≤1, Week 8	28.5% (70)	37.9% (94)	0.028
11	RBS (rectal bleeding sub-score) ≤1, Week 8	58.1% (143)	70.2% (174)	0.006
12	Discontinued corticosteroid use ≥9 days before Week 52 and achieved remission at Week 52	5.7% (8)	13.3% (20)	0.035
13	Discontinued corticosteroid use and achieved sustained remission at both Weeks 32 and 52	1.4% (2)	10.0% (15)	0.002
14	IBDQ responders at Week 52	16.3% (40)	26.2% (65)	0.007
15	IBDQ responders at Week 8	45.5% (112)	58.1% (144)	0.006

Study 827, CSR p 354/3632

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APPENDIX 7: Selected Subgroup Analyses

Study 826: Induction of Clinical Remission (Week 8)

Table 25. Subgroup Analyses: Induction of Clinical Remission (Week 8) [Study 826]

Subgroup	Placebo	Humira 160/80/40	Difference (Humira-Placebo)
Gender			
Male	7/82 (8.5%)	13/83 (15.7%)	7.2%
Female	5/48 (10.4%)	11/47 (23.4%)	13.0%
Age			
<40	9/72 (12.5%)	16/74 (21.6%)	9.1%
40-64	3/54 (5.6%)	7/51 (13.7%)	8.1%
≥65	0/4 (0.0%)	1/5 (20.0%)	20.0%
Race			
White	10/117 (8.5%)	22/119 (18.5%)	10.0%
Non-white	2/13 (15.4%)	2/11 (18.2%)	2.8%
Weight			
< 70 kg	5/35 (14.3%)	11/45 (24.4%)	10.1%
≥70 kg	7/95 (7.4%)	13/85 (15.3%)	7.9%
CRP			
<10.0 mg/L	7/95 (7.4%)	21/101 (20.8%)	13.4%
≥10.0 mg/L	4/32 (12.5%)	2/25 (8.0%)	-4.5%
Smoker			
Ex-smoker	2/35 (5.7%)	6/37 (16.2%)	10.5%
Smoker	0/7 (0.0%)	4/12 (33.3%)	33.3%
Non-smoker	10/88 (11.4%)	14/81 (17.3%)	5.9%
Corticosteroid Use at baseline			
Yes	8/89 (9.0%)	12/71 (16.9%)	7.9%
No	4/41 (9.8%)	12/59 (20.3%)	10.5%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	2/52 (3.8%)	8/51 (15.7%)	11.9%
No	10/78 (12.8%)	16/79 (20.3%)	7.5%

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Study 827: Induction of Clinical Remission (Week 8)

Table 26. Subgroup Analyses: Induction of Clinical Remission (Week 8) [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	7.6%
Female	10/94 (10.6%)	18/106 (17.0%)	6.4%
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	10.1%
40-64	13/116 (11.2%)	17/105 (16.2%)	5.0%
≥65	2/12 (16.7%)	1/7 (14.3%)	-2.4%
Race			
White	23/234 (9.8%)	38/236 (16.1%)	6.3%
Non-white	0/12 (0.0%)	3/12 (25.0%)	25.0%
Weight			
< 70 kg	7/91 (7.7%)	16/95 (16.8%)	9.1%
≥70 kg	16/155 (10.3%)	25/153 (16.3%)	6.0%
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	10.3%
Yes	7/101 (6.9%)	9/98 (9.2%)	2.3%
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	7.6%
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	5.1%
Smoker			
Ex-smoker	7/88 (8.0%)	15/94 (16.0%)	8.0%
Smoker	2/19 (10.5%)	2/20 (10.0%)	-0.5%
Non-smoker	14/138 (10.1%)	24/134 (17.9%)	7.8%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	-2.1%
No	11/166 (6.6%)	29/155 (18.7%)	12.1%
Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	11.4%
No	10/106 (9.4%)	10/98 (10.2%)	0.8%

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Study 827: Clinical Remission at Week 52

Table 27. Clinical Remission at Week 52 [Study 827]

Subgroup	Placebo	Humira	Difference (Humira-Placebo)
Gender			
Male	18/152 (11.8%)	23/142 (16.2%)	4.4%
Female	3/94 (3.2%)	20/106 (18.9%)	15.7%
Age			
<40	11/118 (9.3%)	27/136 (19.9%)	10.6%
40-64	9/116 (7.8%)	16/105 (15.2%)	7.4%
≥65	1/12 (8.3%)	0/7 (0.0%)	-8.3%
Race			
White	21/234 (9.0%)	38/236 (16.1%)	7.1%
Non-white	0/12 (0.0%)	5/12 (41.7%)	41.7%
Weight			
< 70 kg	5/91 (5.5%)	20/95 (21.1%)	15.6%
≥70 kg	16/155 (10.3%)	23/153 (15.0%)	4.7%
Prior Anti-TNF Treatment			
No	18/145 (12.4%)	33/150 (22.0%)	9.6%
Yes	3/101 (3.0%)	10/98 (10.2%)	7.2%
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	8.7%
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	8.0%
Smoker			
Ex-smoker	9/88 (10.2%)	12/94 (12.8%)	2.6%
Smoker	0/19 (0.0%)	5/20 (25.0%)	25.0%
Non-smoker	12/138 (8.7%)	26/134 (19.4%)	10.7%
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	8/80 (10.0%)	17/93 (18.3%)	8.3%
No	13/166 (7.8%)	26/155 (16.8%)	9.0%
Corticosteroid Use at baseline			
Yes	10/140 (7.1%)	25/150 (16.7%)	9.6%
No	11/106 (10.4%)	18/98 (18.4%)	8.0%

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APPENDIX 8: Pertinent Safety Data

SAE's (Induction Set):

Table 28. Serious Adverse Events by System Organ Class, Induction Set

System Organ Class	Placebo N=483	Humira 80/40 N=130	Humira* 160/80/40 N=480
Blood and lymphatic system disorders	2 (0.4)	0	2 (0.4)
Cardiac disorders	0	0	1 (0.2)
Gastrointestinal disorders	29 (6.0)	3 (2.3)	16 (3.3)
Infections and infestations	8 (1.6)	2 (1.6)	3 (0.6)
Investigations	1 (0.2)	0	
Neoplasms benign, malignant and unspecified	2 (0.4)	0	0
Nervous System Disorders		0	1 (0.2)
Psychiatric Disorders	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	1 (0.2)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	3 (0.6)	0	1 (0.2)
Skin and subcutaneous tissue disorders	4 (0.8)	0	1 (0.2)
Vascular disorders	2 (0.4)	0	2 (0.4)

Source: ISS Table 25, p 49/139

Reference ID: 3200370

SAE's (All Humira Set):

Table 29. SAEs Reported by ≥2 Patients, All Humira Set

System Organ Class Preferred Term	Humira 40 mg ew N=402	Humira 40 mg eow N=608	All Humira N=1,010
	n (%)		
Any SAE	90 (22.4)	133 (21.9)	223 (22.1)
Blood and lymphatic system d/o			
Anemia	5 (1.2)	2 (0.3)	7 (0.7)
Cardiac disorders			
Coronary artery disease	1 (0.2)	2 (0.3)	3 (.03)
Gastrointestinal disorders			
Abdominal pain	1 (0.2)	3 (0.5)	4 (0.4)
Colitis	2 (0.5)	1 (0.2)	3 (0.3)
Ulcerative colitis	44 (10.9)	51 (88.4)	95 (9.4)
Crohn's disease	2 (0.5)	0	2 (0.2)
Gastrointestinal dysplasia	0	2 (0.3)	2 (0.2)
Inguinal hernia	2 (0.5)	1 (0.2)	3 (0.3)
Large intestine perforation	0	2 (0.3)	2 (0.2)
Peritonitis	0	2 (0.3)	2 (0.2)
Rectal hemorrhage	0	2 (0.3)	2 (0.2)
Small intestinal obstruction	1 (0.2)	1 (0.2)	2 (0.2)
General disorders and administration site conditions			
Noncardiac chest pain	1 (0.2)	1 (0.2)	2 (0.2)
Hepatobiliary disorders			
Cholelithiasis	1 (0.2)	1 (0.2)	2 (0.2)
Infections and infestations			
Abdominal abscess	0	3 90.5)	3 (0.3)
Anal abscess	0	4 (0.7)	4 (0.4)
Appendicitis	3 (0.7)	5 (0.8)	8 (0.8)
Cytomegalovirus colitis	1 (0.2)	1 (0.2)	2 (0.2)
Herpes zoster	1 (0.2)	2 (0.3)	3 (0.3)
Lobar pneumonia	3 (0.7)	1 (0.2)	4 (0.4)
Perirectal abscess	2 (0.5)	0	2 (0.2)
Respiratory tract infection	1 (0.2)	1 (0.2)	2 (0.2)
Investigations			
Weight decreased	1 (0.2)	1 (0.2)	2 (0.2)
Musculoskeletal and connective tissue d/o			
Arthralgia	2 (0.5)	0	2 (0.2)
Backpain	0	2 (0.3)	2 (0.2)
Intervertebral disc protrusion	0	2 (0.3)	2 (0.2)
Osteoarthritis	0	4 (0.7)	4 (0.4)
Neoplasms benign, malignant, and unspecified			
B-cell lymphoma	1 (0.2)	2 (0.3)	3 (0.3)
Uterine leiomyoma	1 (0.2)	1 (0.2)	2 (0.2)
Renal and urinary disorder			
Nephrolithiasis	0	2 (0.3)	2 (0.2)
Renal failure acute	2 (0.5)	0	2 (0.2)
Respiratory, thoracic, and mediastinal d/o			
Pulmonary embolism	1 (0.2)	1 (.2)	2 (.2)
Surgical and medical procedures			
Abortion induced	0	3 (0.5)	3 (0.3)
Vascular disorders			
Deep vein thrombosis	3 (0.7)	2 (0.3)	5 (0.5)

4-Month Safety Update p.189-191, Table 24

Reference ID: 3200370

Common AE's (Induction Set):

Table 30. TEAEs Reported by ≥2% of Patients, Induction Set

MedDRA System Organ Class / Preferred Terms	Placebo N=483	Humira 80/40 N=120	Humira 160/80/40 N=480	Total Humira N=600
	n(%)			
Blood and lymphatic system disorders				
Anemia	14 (2.9)	2 (1.5)	9 (1.9)	11(1.8)
Gastrointestinal Disorders				
Abdominal Pain	15 (3.1)	3 (2.3)	6 (1.3)	9 (1.5)
Abdominal tenderness	5 (1.0)	3 (2.3)	3 (0.6)	6 (1.0)
Colitis Ulcerative	59 (12.2)	10 (7.7)	35 97.3)	45 (7.4)
Dyspepsia	6 (1.2)	3 (2.3)	8 (1.7)	11 (1.8)
Nausea	16 (3.3)	4 (3.1)	10 (2.1)	14 (2.3)
Toothache	0	3 (2.3)	2 (0.4)	5 (0.8)
General Disorders and Administration Site Conditions				
Fatigue	12 (2.5)	2 (1.5)	18 (3.8)	20 (3.3)
Influenza like illness	10 (2.1)	2 (1.5)	1 (0.2)	3 (0.5)
Injection site pain	11 (2.3)	2 (1.5)	12 (2.5)	14 (2.3)
Pyrexia	14 (2.9)	3 (2.3)	8 (1.7)	11 (1.8)
Infections and Infestations				
Influenza	8 (1.7)	3 (2.3)	3 (0.6)	6 (1.0)
Nasopharyngitis	23 (4.8)	6 (4.6)	26 (5.4)	32 (5.2)
Upper Respiratory Infection	12 (2.5)	6 (4.6)	5 (1.0)	11 (1.8)
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	9 (1.9)	5 (3.8)	10 (2.1)	15 (2.5)
Nervous System Disorders				
Headache	42 (8.7)	9 (6.9)	20 (4.2)	29 (4.8)
Psychiatric Disorders				
Insomnia	10 (2.1)	1 (0.8)	5 (1.0)	6 (1.0)
Skin and subcutaneous Tissue Disorders				
Acne	6 (1.2)	3 (2.3)	9 (1.9)	12 (2.0)
Erythema	2 (0.4)	3 (2.3)	8 (1.7)	11 (1.8)
Rash	5 (1.0)	5 (3.8)	4 (0.8)	9 (1.5)

Adapted from Applicant's Table 42, ISS p 203-204/5677

Common AE's (Maintenance Set):

Table 31. Common AEs, Maintenance Set

MedDRA Preferred Term	Placebo N=224	Humira 160/80/40 N=232
	N (%)	
Any Adverse Event	152 (68.2)	172 (73.5)
Colitis ulcerative	37 (16.6)	39 (16.7)
Nasopharyngitis	11 (4.9)	26 (11.1)
Abdominal pain	12 (5.4)	18 (7.7)
Arthralgia	9 (4.0)	17 (7.3)
Headache	15 (6.7)	11 (4.7)
Nausea	12 (5.4)	9 (3.8)

Source: Table 16, ISS

Reference ID: 3200370

Common AE's (All Humira Set):

Table 32. Common AEs, All Humira Set

MedDRA System Organ Class Preferred Terms	
	n (%)
Blood and lymphatic system disorders	
Anemia	61 (6.0%)
Gastrointestinal Disorders	
Abdominal Pain	70 (6.9%)
Colitis Ulcerative	321 (31.8%)
Nausea	73 (7.2%)
General Disorders and Administration Site Conditions	
Fatigue	79 (7.8%)
Pyrexia	62 (6.1%)
Infections and Infestations	
Nasopharyngitis	169 (16.7%)
Upper Respiratory Tract Infection	83 (8.2%)
Sinusitis	59 (5.8%)
Bronchitis	50 (5.0)
Musculoskeletal And Connective Tissue Disorders	
Arthralgia	105 (10.4%)
Back Pain	56 (5.5%)
Nervous System Disorders	
Headache	98 (9.7%)
Respiratory Tract Disorders	
Cough	63 (6.2%)
Oropharyngeal Pain	58 (5.7%)
Skin and subcutaneous Tissue Disorders	
Rash	62 (6.1%)

Source: Table 20, ISS

Reference ID: 3200370

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA Efficacy Supplement Resubmission
Application Number(s)	sBLA 125057/232
Priority or Standard	Standard
Submit Date(s)	30 Mar 2012
Received Date(s)	30 Mar 2012
PDUFA Goal Date	28 Sep 2012
Division / Office	DGIEP/ODEIII
Reviewer Name(s)	Klaus Gottlieb, MD, MS, MBA
Review Completion Date	27 SEP 2012
Established Name	adalimumab
(Proposed) Trade Name	Humira
Therapeutic Class	TNF-alpha-blocker
Applicant	Abbott
Formulation(s)	subcutaneous
Dosing Regimen	160 mg/ 80 mg.
Indication(s)	Ulcerative Colitis
Intended Population(s)	Moderate to severe UC

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that Humira be approved for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). This recommendation is based on a review of the original prior-approval efficacy supplement to the BLA (sBLA) for Humira (adalimumab) that was initially submitted on January 25, 2011, the resubmission, received March 30, 2012, which is the sponsor's response to FDA's Complete Response (CR) letter, and deliberations during the Gastrointestinal Drug Advisory Committee (GIDAC) August 28, 2012 in Silver Spring, MD, as well as internal meetings with the review team.

1.2 Risk Benefit Assessment

Moderately to severely active ulcerative colitis (UC) is a serious chronic condition, which significantly affects the quality of life and long-term health status of patients. When pharmacological therapies fail, colectomy may be required.

Remicade (infliximab) is currently the only FDA-approved therapeutic option for patients with moderate to severe UC who have failed conventional therapies. It is an effective treatment, but has serious known risks that are not specific to infliximab but apply to other TNF-alpha-blockers as well.

Conventional treatment options for patients with UC consist of aminosalicylates, corticosteroids and immunosuppressants. When these fail, the remaining options are limited. A second TNF-alpha blocker option would therefore be valuable if risks are balanced by efficacy.

The induction of remission studies (826, 827) had limitations which were detailed before and provided evidence of only a modest or marginal population effect (< 10% over placebo) on induction of remission. This reviewer and other members of the review team questioned the clinical meaningfulness of the magnitude of the observed treatment difference.

There was only one maintenance study. It was designed to measure "sustained clinical remission", not "maintenance of remission" because patients who achieved clinical remission during the induction phase continued on the respective treatment instead of being rerandomized to placebo or Humira. The maintenance study (study 827) suggests only a weak effect (<5% over placebo) in the population. The reviewers questioned the clinical meaningfulness of the magnitude of the observed treatment difference.

As we are evaluating the clinical meaningfulness of the effect size of drugs, it is natural to do so considering our historical experience with similar drugs for the same indication. Despite many caveats, it can reasonably be stated that study ACT 1 that evaluated induction of remission in patients with moderately to severe ulcerative colitis with Remicade (infliximab) and study 826 (adalimumab) were similar in design and demographic factors. ACT 1 had clinical response and not clinical remission as the primary endpoint, and the placebo response rate in ACT 1 was slightly higher. Also, in study 826 there appeared to be more patients that were not on steroids or immunosuppressants upon entry. The effect size for the induction of remission was 23.9 % for infliximab (95% CI: 13.0% -34.6%) and 9.3 % (95% CI: CI 0.8% - 17.9%) for adalimumab.

Although limited, the data in study 827 suggest that there is no advantage of Humira for induction of clinical remission in patients who lost response to or were intolerant to another TNF blocker; patients in this subgroup did not appear to achieve induction of clinical remission at a higher rate with Humira than with placebo.

Based on intensive discussions over the last several months the review team and this reviewer have identified a number of recommended postmarketing requirements and commitments.

1. A study to bank samples for future evaluation to identify genetic mutations and other biomarkers that predispose inflammatory bowel disease (IBD)patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).
2. A multi-center study of Humira in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting to assess the long-term safety of serious infections and malignancies and long-term effectiveness in a comparative registry.
3. A safety and pharmacokinetic trial as a substudy of the trial described in #4 to evaluate trough concentrations and antibody levels at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission.
4. A trial to evaluate efficacy and safety of induction regimens at doses higher than 160/80 mg. In this trial, the efficacy of adalimumab should be assessed with induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure response analysis. Also, collect immunogenicity samples and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety.
5. Development, qualification, and validation of an improved anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference.
6. Utilizing a validated AAA assay as described in PMC #5 above, the sponsor should assess the immunogenicity profile based on post-dose patient samples

from completed study M10-223, the trial conducted under #4, the trial conducted under #7, and other future studies from other regions of the world in this disease population.

7. A one-year, multi-center, randomized, double-blind placebo controlled trial to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis

The known serious safety concerns of Humira are well-characterized. The overall safety profile of Humira is comparable to other TNF-blockers, but does not provide a safety advantage over the currently marketed therapeutic option, Remicade.

Given this background, the Division of Gastroenterology and Inborn Errors Products convened a Gastrointestinal Drug Advisory Committee (GIDAC) meeting for August 28, 2012. The questions most relevant to this section were:

1. Do the observed treatment differences (Humira 160/80/40 versus placebo) in the proportion of patients that had clinical remission at Week 8 of 9.3% (95% CI: 0.8%, 17.9%) (Study 826) and 7.2% (95% CI: 1.3%, 13.2%) (Study 827) represent a clinically meaningful benefit?
2. Does the observed treatment difference in the proportion of patients that had clinical remission at both Weeks 8 and 52 of 4.4% (95% CI: 0.1%, 9.0%) (Study 827) represent a clinically meaningful benefit?
3. Do the expected benefits outweigh the known and potential risks of Humira for the treatment of patients with moderately to severely active UC based on currently available data?

The majority of the votes were yes to all three questions (Question 1: Yes: 15, No: 1, Abstain:1; Question 2: Yes: 16, No: 1, Abstain:0; Question 3: Yes:15,No:2, Abstain:0). Details of the discussion will be reviewed elsewhere in this document.

This reviewer's assessment of the risk-benefit assessment for Humira for an ulcerative colitis indication was skeptical prior to the GIDAC and changed to favorable afterwards based on the input of other practicing gastroenterologists and experts in the field of Inflammatory Bowel Disease. This reviewer accepts the judgment of the GIDAC panel in regards to the important question of clinical meaningfulness and overall/risk benefit and recommends approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No new or unexpected safety concerns were seen during the Humira UC studies that would require additional risk management for this new indication of Humira. A boxed warning as in the current Humira label and continued surveillance are still deemed necessary.

1.4 Recommendations for Postmarket Requirements and Commitments

The GIDAC panel recommended that the efficacy of higher doses of Humira should be examined. The panel also wanted to see studies which will explore when to introduce a drug of this class, who is likely to benefit, and reasons for loss of response, (i.e. immunogenicity or dose related). This research topic is essentially similar to this reviewer's question (section 1.2) how Humira may be best used in patients who are naïve to TNF-alpha blockers or those who are currently on a TNF-alpha-blocker and want or need to switch. This reviewer agrees with these recommendations. A cohort study correlating patients response and remission status with drug and antibody levels could be a component of such a study.

Additional postmarketing studies should include the evaluation of efficacy in children and adolescents (the Pediatric Research Equity Act of 2003 (PREA) does not apply due to the orphan status of the drug) and a long-term registry or observational cohort study exploring the risk of being on Humira vs. immunosuppressants.

2 Introduction and Regulatory Background

This review is to be understood as an addendum to the 1st cycle Clinical Review and will only present information that is either new in this 2nd review cycle, is interpreted differently or is necessary for context so that this review may be use as a stand-alone-document.

2.1 Product Information

Ulcerative colitis (UC) and Crohn's (CD) disease are distinct pathophysiological entities with overlapping manifestations, predisposing factors and treatment modalities. They are often discussed together as inflammatory bowel disease (IBD) which minimizes important distinctions. In those geographic areas where both diseases are prevalent, especially North America and Europe, UC has a higher incidence (1.2 to 20.3 cases per 100,000 persons per year) than Crohn's disease (0.03 to 15.6 cases per 100,000 persons per year). Unlike CD which affects the entire bowel wall, UC is limited to the mucosa (epithelium), generally milder, with fewer resultant complications except for epithelial cancer, i.e., adenocarcinoma of the colon.

UC manifests itself by bloody diarrhea with or without mucus. The disease tends to be most severe in the rectum and sigmoid but can affect the entire colon. Because of this severity gradient sigmoidoscopy is a good gauge of mucosal disease activity. In contrast, CD can affect any part of the entire GI tract and frequently spares long segments of the colon or small bowel ("skip lesions").

In UC, depending on the extent of the disease malaise, fever and weight loss, diarrhea, frequent evacuations of blood and mucus, urgency or tenesmus, and abdominal pain may be encountered. Complications are either acute or chronic. Chronic complications are extraintestinal organ manifestations such as primary sclerosing cholangitis and colon cancer and acute complications, mostly are severe bleeding or toxic megacolon in fulminant disease. Both are fortunately rare.

Decisions about treatment of UC weigh such factors as disease activity, disease extent and duration, previous treatment attempts and patient's preference into account.
The goal is to stop the patient's active acute disease (induction of remission) and then maintain the patient in remission. 5-ASA preparations, given orally, rectally or in combination, are the first line of treatment for induction of remission. Patients with mild-to-moderate ulcerative colitis that is refractory to rectal therapies and to oral 5-aminosalicylate are often advanced to oral glucocorticoids and immunosuppressive agents (azathioprine or 6-mercaptopurine).

Patients who continue to require glucocorticoid therapy or those who do not respond to it are candidates for TNF-alpha-antagonists. Currently only infliximab (Remicade) is marketed for this indication.

Adalimumab is a humanized IgG monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors, which in turn inhibits TNFα-induced pro-inflammatory effects.

Humira was originally approved for rheumatoid arthritis in 2002. Since then, it has also been found to be effective in treating several other diseases, and it is currently also approved for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis.

Humira has no specific contraindications. The approved labeling has a boxed warning for serious infections and malignancies, which is part of TNFα-antagonist class labeling. The following serious adverse reactions are highlighted in the boxed warming for serious infections: tuberculosis, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens. The following serious adverse reactions are highlighted in the boxed warming for malignancies: hepatosplenic T-cell lymphoma (HSTCL) and other lymphomas and malignancies. There are also warnings and precautions for hypersensitivity reactions, Hepatitis B virus reactivation, demyelinating disease, cytopenias, use with anakinra, heart failure, autoimmunity, use with live vaccines, and use with abatacept.

2.2 Tables of Currently Available Treatments for Proposed Indications

Only infliximab (Remicade) is currently marketed for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

See 1st cycle review.

2.4 Important Safety Issues With Consideration to Related Drugs

As a class TNF-alpha blockers share safety issues (see section 2.1 in this document and 1st cycle review).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- June 15, 2006 Pre-IND / Pre-Phase 3 Meeting
- November 23, 2010 Pre-sBLA Meeting
- January 25, 2011 sBLA Original Submission
- November 21, 2011 CR Action
- March 30, 2012 sBLA Re-Submission

2.6 Other Relevant Background Information

On November 21, 2001 a Complete Response (CR) letter was sent to the sponsor. This letter is in the appendix. The most relevant questions for this review are quoted:

> CLINICAL
> 1. Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are two- fold.
>
> First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not

significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

Second, we are concerned that you may not have adequately selected an appropriate adalimumab dose for your pivotal efficacy trials. We note the modest improvement in clinical remission rates reported in both trials (treatment differences relative to placebo in clinical remission at Week 8 of 9.3% and 7.2% in Studies M06-826 and M06-827, respectively), and the treatment difference relative to placebo in sustained clinical remission (at both Weeks 8 and 52) of 4.4% in Study M06-827.

To address these concerns, we will need to seek expert advice at a future meeting of the Gastrointestinal Drugs Advisory Committee.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No concerns. See 1st cycle review.

3.2 Compliance with Good Clinical Practices

No concerns. See 1st cycle review. It should be noted, that the FDA Briefing Document for the Advisory Committee called out one particular subject from the Humira group that may have been misclassified as a remitter. However, after receipt of additional clinical information on this case shortly before the Advisory Committee, this Clinical Reviewer concluded that this patient is indeed a remitter.

3.3 Financial Disclosures

No concerns. See 1st cycle review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Unchanged. See 1st cycle review.

4.2 Clinical Microbiology

Unchanged. See 1st cycle review.

4.3 Preclinical Pharmacology/Toxicology

Unchanged. See 1st cycle review.

4.4 Clinical Pharmacology

Unchanged. See 1st cycle review. Here summarized to give important context.

The available exposure-response data in patients with UC indicate that the dosing regimen for induction phase has not been fully explored. Exposure-response analysis was conducted (using data from Study 827[1]) to evaluate the adequacy of the proposed induction and maintenance doses.

Induction: The exposure-response analysis suggested that a higher induction dose could achieve a greater treatment effect for the induction of clinical remission at Week 8 because of the following observations:

(a) There was an increased remission rate with increased exposures that did not plateau at higher exposures. A statistically-significant (p=0.0002) relationship was established between adalimumab Week 8 trough concentration and clinical remission at Week 8 using logistic regression.
(b) Patients with lower exposures in the induction phase exhibited inadequate response (and switched to open label treatment) earlier than patients with higher exposures.

Maintenance: A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data.

In light of the modest treatment effect for induction of clinical remission, the exposure-response findings contributed to the concern that the induction dose studied in the two clinical trials may not be optimal.

[1] Study 827 was the only study in which PK data were collected.

5 Sources of Clinical Data

The sponsor did not submit new studies or clinical trial data for this resubmission. Instead, numerous post-hoc analyses were performed on the data and these will be reviewed in this document.

5.1 Tables of Studies/Clinical Trials

The table below summarizes the clinical trials submitted in support of the current application. Note that in addition to Studies 826 and 827, there was a long-term single-arm, open-label trial (Study 223) that is currently ongoing.

Table 1: Overview of Studies 826 and 827

Study	Design	Population	Treatment Duration	Treatment Arms
826 (Induction of Remission Trial)	R, DB, PC	▪ Moderately to severely active UC*	8 weeks	➢ Humira 160/80/40[#] (n=130[‡]) ➢ Humira 80/40[†] (n=130[‡]) ➢ Placebo (n=130[‡])
827 (Induction and Sustained Remission Trial)	R, DB, PC	▪ Moderately to severely active UC* ▪ Prior TNFα-antagonist users (40%)	52 weeks	➢ Humira 160/80/40[#] (n=258) ➢ Placebo (n=260)
223 (Extension Study)	OL	▪ Continuation from Studies 826 and 827	240 weeks planned (ongoing)	➢ Humira 40 EOW or EW (n=592[§])

*Humira 160/80/40 SC EOW: 160 mg at Wk 0, 80 mg at Wk 2, and 40 mg at Wk 4 and every other wk
[#]Humira 80/40 SC EOW: 80 mg at Wk 0, 40 mg at Wk 2 and every other wk
[†]Humira 40 mg SC EOW: 40 mg every other wk
[‡]Humira 40 mg SC EOW/EW: every other wk or every wk
[§] Data cutoff date of December 16, 2011. 592 enrolled (349 receiving 40 mg EOW and 243 receiving 40 mg EW); 384 ongoing (255 receiving 40 mg EOW and 129 receiving 40 mg EW); escalation from EOW to EW allowed during study for inadequate response.
For Study 826, the number of patients enrolled is shown as ITT-E (ITT-A3); the definitions of ITT-E and ITT-A3 are provided in Appendix 3.

5.2 Review Strategy

As mentioned, the sponsor did not submit new studies or clinical trial data for this resubmission. Instead, numerous exploratory analyses were performed on the data and these will be reviewed in this document. Some of the exploratory data analysis by the

sponsor endeavor to combine safety and efficacy data in one metric or statistic. While these analyses could be listed either under efficacy or safety, this reviewer will discuss them under safety.

5.3 Discussion of Individual Studies/Clinical Trials

In this document, only the new post-hoc analyses submitted in support of the resubmission will be reviewed. For a detailed review of the clinical trial data of studies 826 and 827, refer to the 1st cycle review.

6 Review of Efficacy (Additional Analyses submitted in Response to CR Letter)

6.1 Exploratory Analyses Overview

The applicant conducted several exploratory analyses of data from Studies 826 and 827.

The Applicant proposed that these exploratory analyses:

- examine the totality of the efficacy data,
- demonstrate the clinical relevance and robustness of the efficacy data, and
- support a favorable benefit/risk profile for the dosing regimen studied.

Because of the concerns stated in the CR Letter (i.e., Study 826 results are sensitive to alternative analyses and the conclusions are not considered robust from a statistical perspective, the appropriate dose may not have been selected for the two studies, and the improvements in the rates of clinical remission at Week 8 and sustained clinical remission at Weeks 8 and 52 reported relative to placebo were modest), the Clinical and Statistical Reviewers examined these data to determine if there is evidence of a clinically meaningful benefit.

The Clinical and Statistical Reviewers concluded the following regarding the exploratory analyses:

- The exploratory analyses were difficult to interpret because neither the endpoints nor the comparisons were prospectively defined in an analysis plan.
- The exploratory analyses did not adequately address the concerns from the original review.

The specific exploratory analyses submitted by the Applicant in the resubmission included the following:

- primary and secondary analyses of Study 826 using the ITT-E population (i.e., all patients enrolled that received study drug or placebo);
- integrated primary and secondary analyses across Studies 826 and 827;
- additional exploratory analyses from Study 827 (e.g., clinical response based on partial Mayo score at Weeks 2, 4, and 8 and clinical response based on full Mayo score at Week 8);
- re-analysis of full and partial Mayo scores at Baseline and Week 52 using average of last 3 days (rather than standard "worst-ranked" methodology)-Study 827;
- all-cause and UC-related hospitalizations (pooled across Studies 826 and 827); and
- exploratory analyses of clinical remission and clinical response status at Week 52 in the subgroup of patients from Study 827 in clinical response at Week 8.

The following analyses were conducted by the sponsor in an attempt to combine safety and efficacy data and will be reviewed in section 7.

- serious adverse event (SAE)-adjusted days in remission
- number of patients who discontinued due to adverse events (AEs) relative to number of patients in remission at Weeks 8 and 52
- Net Efficacy Adjusted Risk (NEAR) analysis
- Number Needed to Harm (NNH) analyses

The exploratory analysis of dose escalation from EOW to EW in the open label Study 223 (submitted as part of the Study 223 Interim Clinical Study Report) is also included in this section.

Due to the exploratory nature of these analyses, the p-values presented are presented for reference only and not intended to represent any formal statistical testing or basis for statistical inference.

6.2 Exploratory Analyses in Detail

Exploratory Analysis #1 (Applicant): Adjustment for Baseline Mayo Score

Exploratory Analysis #1 is summarized in the table below. This was submitted by the Applicant in the current review cycle in response to the Statistical Reviewer's analysis in the first review cycle (also described in the table below).

Table 2: Exploratory Analysis #1 (Applicant): Adjustment for Baseline Mayo Score (Study 826 Primary Endpoint)

Analysis	Description	p-value
Original (for reference)	▪ Did not adjust for Baseline Mayo Score ▪ Used the chi-squared test	0.031
FDA Statistical Reviewer (1st cycle)	▪ Adjusted for Baseline Mayo Score (categorizing by score)* ▪ Used the CMH test	0.0852
#1a (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by quartiles)# ▪ Used the CMH test	0.034
#1b (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by tertiles)# ▪ Used the CMH test	0.034
#1c (Applicant)	▪ Adjusted for Baseline Mayo Score (categorizing by median)# ▪ Used the CMH test	0.028

CMH: Cochran-Mantel-Haenszel
*See Section 4.5 of this Briefing Document (Robustness of Data–Study 826: Adjustment for Baseline Mayo Scores) and Section 4.2 of this Briefing Document
#See Appendix 7 of this Briefing Document.

It should be noted that the Statistical Reviewer's analysis of adjustment for baseline Mayo scores was cited in the CR Letter as an example of the results being sensitive to alternative analyses. The additional analyses by the Applicant are alternative ways to adjust for baseline Mayo score but are less sensitive than the Statistical Reviewer's method. Moreover, these results are hypothesis generating as the methods of categorization (by quartiles, tertiles, and median) were not pre-specified.

Exploratory Analysis #2 (Applicant): Week 8 Remission Rates Across Analysis Populations

Exploratory Analysis #2 is summarized in the table below. The pre-specified analysis populations for Study 826 and Study 827 were the ITT-A3 and ITT populations, respectively. In addition to these analysis populations, the Applicant provided Week 8 Clinical Remission rates for additional analysis populations (ITT-E, previously defined; ITT-non-A3 and IAS-E, defined in the table below).

Table 3: Exploratory Analysis #2 (Applicant): Week 8 Remission Rates Across Analysis Populations (Study 826)

Study	Analysis Population	Placebo N	Humira 160/80/40 N	Rate (95% CI)	p-value
826	ITT-A3	130	130	**9.2** (0.9, 17.6)	0.031
826	ITT-non-A3*	92	93	**7.5** (-0.3, 15.3)	0.062

826	ITT-E	222	223	**8.5** (2.6, 14.4)	0.005
827	ITT	246	248	**7.1** (1.2, 12.9)	0.019
826, 827	IAS-E[#]	468	470	**8.1** (3.8, 12.1)	<0.001

The ITT-A3 and ITT-E populations of Study 826 were defined previously.
*The ITT-non-A3 population is defined as the population prior to Amendment 3 that received Humira or placebo.
[#]The IAS-E population (Induction and Maintenance Analysis Set) includes the ITT-E population of 826 and the ITT population of 827
(Table above is summarized from Figure on Page 47 of the March 30, 2012 sBLA Resubmission.)

The Clinical Reviewer and Statistical Reviewer concluded that the results from the additional analysis populations (i.e., ITT-non-A3, ITT-E, and IAS-E) are post hoc and do not alleviate concerns of the pre-specified analyses.

Exploratory Analysis #3 (Applicant): Primary and Secondary Analyses of Study 826 Using the ITT-E and IAS-E Population

Exploratory Analysis #3 is summarized in the tables below. The Applicant provided the primary and secondary analyses of Study 826 using the ITT-E population (as opposed to the ITT-A3 population) and the IAS-E population.

Table 4: Exploratory Analysis #3a (Applicant): Primary and Secondary Analyses of Study 826 Using the ITT-E Population (Study 826)

	Placebo N = 222	ADA 160/80/40 N = 223		Treatment Difference
Endpoint	**n (%)**	**n (%)**	***P* value[a]**	**(%)**
Primary				
Clinical remission per FM	16 (7.2)	35 (15.7)	0.005	8.5
Ranked Secondary				
Clinical response per FM	95 (42.8)	116 (52.0)	0.051	9.2
Mucosal healing (endoscopy subscore ≤ 1)	79 (35.6)	99 (44.4)	0.056	8.8
Rectal bleeding subscore (RBS) ≤ 1	147 (66.2)	162 (72.6)	0.140	6.4
Physician's global assessment (PGA) ≤ 1	98 (44.1)	119 (53.4)	0.050	9.2
Stool frequency subscore (SFS) ≤ 1	81 (36.5)	95 (42.6)	0.185	6.1

FM: Full Mayo Score
a. P value based on CMH test with in/not in the ITT-A3 Analysis Set as the stratification factor.

Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission.
(Table above modified from Page 48 of the sBLA Resubmission dated March 30, 2012)

Table 5: Exploratory Analysis #3b (Applicant): Primary and Secondary Analyses of Studies 826 and 827 Using the IAS-E Population (Studies 826 and 827)

	Placebo		ADA 160/80/40			Treatment Difference
Endpoint	**N**	**n (%)**	**N**	**(%)**	***P* value[a]**	**(%)**
Primary						
Clinical remission per FM	468	37 (7.9)	470	75 (16.0)	< 0.001	8.1
Ranked Secondary						
Clinical response per FM	468	176 (37.6)	470	240 (51.1)	< 0.001	13.5
Mucosal healing (endoscopy subscore ≤ 1)	468	152 (32.5)	470	200 (42.6)	0.002	10.1
RBS ≤ 1	468	286 (61.1)	470	335 (71.3)	0.001	10.2
PGA ≤ 1	468	188 (40.2)	470	232 (49.4)	0.005	9.2
SFS ≤ 1	468	149 (31.8)	470	188 (40.0)	0.010	8.2

FM: Full Mayo Score
a. P value based on CMH test with 3 levels of stratification: 1) subjects in Study M06-826, 2) subjects in Study M06-827 with prior anti-TNF exposure; and 3) subjects in Study M06-827 without prior anti-TNF exposure.
Note: According to the NRI analysis, all missing clinical remission values were considered to be non-remission. (Table above modified from Page 49 of the sBLA Resubmission dated March 30, 2012)

The FDA Clinical Reviewer and FDA Statistical Reviewer concluded that the results from the primary and secondary analyses in the ITT-E and IAS-E populations do not alleviate all concerns regarding the results of the pre-specified primary analyses.

Exploratory Analysis #4 (Applicant): Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Exploratory Analysis #4 is summarized in the table below. The Applicant performed an analysis of the rates of Clinical Remission and Clinical Response at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8.

Table 6: Exploratory Analysis #4 (Applicant): Clinical Remission and Response at Week 52 in Week 8 Clinical Remitters (Study 827)

Analysis	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value*
Original Analysis (for reference): Sustained Clinical Remission (Remission at Wks 8 and 52)	4.1% (10/246)	8.5% (21/248)	4.4%	0.047
#4a: Clinical *Remission* at Week 52 (in Week 8 Clinical Remitters)	43.5% (10/23)	51.2% (21/41)	**7.7%**	**0.618**
#4b: Clinical *Response* at Week 52 (in Week 8 Clinical Remitters)	52.2% (12/23)	63.4% (26/41)	**11.2%**	**0.400**

(Table above summarized from Pages 161-162 of the March 30, 2012 sBLA Resubmission.)

The Clinical Reviewer concluded that the results of the analysis of Clinical Response and Clinical Remission at Week 52 in the subgroup of patients that achieved Clinical Remission at Week 8 are not informative and serve only as an exploratory comparison.

Exploratory Analysis #5 (Applicant): Clinical Response Based on Partial Mayo Score at Weeks 2, 4, and 8

To explore the timing of the onset of Humira, the Applicant explored the clinical response based on partial Mayo (PM) score at Weeks 2, 4, and 8. The analysis revealed that the treatment difference (Humira-placebo) was greatest at Week 2 and smallest at Week 4. However, the clinical response rates increased from Week 2 through Week 8 for both placebo and Humira patients. See Table 7, below.

Table 7: Exploratory Analysis #5 (Applicant): Clinical Response per PM Score at Weeks 2, 4, and 8, and per FM at Week 8, Study 827

Study Visit	Number (%) of Subjects: Placebo N = 246	Number (%) of Subjects: ADA N = 248	Treatment Difference[a] (%)	*P* value[b]
Week 2 PM	49 (19.9)	97 (39.1)	19.2	< 0.001
Week 4 PM	78 (31.7)	113 (45.6)	13.9	0.002
Week 8 PM	86 (35.0)	123 (49.6)	14.6	0.001
Week 8 FM	85 (39.2)	125 (55.6)	16.4	< 0.001

a. Percent difference between active treatment and placebo.

b. *P* value to compare adalimumab with placebo was based on CMH test.

Notes: According to the NRI method, all missing clinical response values were considered to be nonresponses.

Copied and electronically reproduced from Table 18, p 69, March 20, 2012 sBLA Resubmission

The Clinical Reviewer concluded that the analysis of PM scores for Weeks 2 through 8 may suggest that patients respond early to treatment with Humira; however, this analysis does not reveal if patients who respond at Week 2 continue to be in response at Weeks 4 and 8 or if they subsequently lose that response prior to Week 8. Further, the Clinical Reviewer concluded that no statistical inferences can be made due to the exploratory nature of these analyses.

Exploratory Analysis #6 (Applicant): Re-analysis from Study 827 Using Average of Last 3 days (Rather than Standard "Worst-Ranked" Methodology)

In the pre-specified Statistical Analysis Plan (SAP), full Mayo (FM) scores were calculated using worst-rank methodology (i.e., the worst subscore from the past 3 days of the patient subject diary for Stool Frequency Score (SFS) and Rectal Bleeding Score (RBS) was used to calculate the Mayo score for each visit). To evaluate the possible impact of worst score versus average score methodology in Study 827, the Applicant undertook an exploratory analysis of selected patients from sites with readily-available diary data and re-calculated FM scores using the average SFS and RBS subscores from the three days prior to each visit.

To conduct this analysis, the Applicant included patients who had completed Study 827 and were currently participating in the long-term Study 223. The Applicant included three to four patients from each of the thirteen sites who reported still having readily-available diary data of both placebo and Humira patients. In the end, data from only 16 patients was used for this analysis. The results of this exploratory analysis revealed that using the average method to calculate SFS and RBS (instead of the worst-rank method) may have resulted in Week 52 FM and PM scores that were 0.59 points lower. See Table 8, below.

Table 8: Exploratory Analysis #6: Full Mayo (FM) and Partial Mayo (PM) Scores Using Worst-case vs. Average Scores, Study 827

	Baseline	Week 52	Δ[a]	Overall Δ[b]
FM Scores				
ADA, N = 9				
Worst score from the past 3 days	9.11	2.89	6.22	
Average score from the past 3 days	9.00	2.33	6.67	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	9.57	4.29	5.28	
Average score from the past 3 days	9.00	3.86	5.14	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**
PM Scores				
ADA, N = 9				
Worst score from the past 3 days	6.44	2.00	4.44	
Average score from the past 3 days	6.33	1.44	4.89	
Difference between Δ of worst score and average score[b]				–0.45
Placebo, N = 7				
Worst score from the past 3 days	6.86	2.86	4.00	
Average score from the past 3 days	6.29	2.43	3.86	
Difference between Δ of worst score and average score[b]				0.14
Absolute Difference between Adalimumab and Placebo				**0.59**

a. Δ – Difference between scores at Baseline and Week 52.
b. Overall Δ – difference between Δ of the worst score and average score.

Copied and electronically reproduced from Table 11, p 59, sBLA Resubmission dated March 30, 2012.

The analysis was completed with data from only 16 of the 494 patients who participated in Study 827. The Clinical Reviewer concluded that with such a small sample size, no meaningful information can be obtained. In addition, the Clinical Reviewer concluded that these data cannot be relied upon for statistical inference given their *post-hoc* nature.

Exploratory Analysis #7 (Applicant): All-Cause and UC-related Hospitalizations (Pooled Across Studies 826 and 827)

In a further exploratory analysis, the Applicant presented pooled data from Studies 826 and 827 to evaluate hospitalization rates with active drug and placebo. As previously pointed out, these two studies had significant design differences that make pooling of data for efficacy analysis highly problematic. The chief concerns are that patients in Study 826 were naïve to TNF-alpha-antagonists whereas 40 % of subjects in Study 827

Reference ID: 3196365

were anti-TNF-experienced. Moreover, a protocol change (Amendment 3) in Study 826 led to the addition of the lower dose treatment arm. The hospitalizations of these patients were not used for the Applicant's hospitalization analysis because they "did not perform significantly better than subjects randomized to placebo for the primary endpoint."[2] Whether this is a valid reason is arguable: (1) This is a post-hoc justification; (2) a lower dose may not translate into an improvement in the Mayo score (primary endpoint), however, it may stabilize the patient enough to prevent a hospitalization.

While the Applicant presents data from several different sensitivity analyses which support their general conclusion (patients on active drug have fewer hospitalizations), other types of sensitivity analyses are not given: For example, results broken out by individual studies (826 and 827 not pooled) would be of interest and also an analysis that keeps patients on the low dose arm in Study 826 (pre-amendment) in the analysis.

The tables below are given for the purpose of reference.

Table 9: Exploratory Analysis 7a: All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

	n/PYs at Risk[a] (%)		Relative Risk of	
Outcome	ADA 160/80/40[b] N = 471	Placebo N = 468	ADA/Placebo (95% CI)	*P* value[c]
All-cause hospitalization	67/379 (18)	56/214 (26)	0.7 (0.5, 1.0)	0.030
UC-related hospitalization	45/389 (12)	47/216 (22)	0.5 (0.4, 0.8)	0.002
UC- or drug-related hospitalization	53/385 (14)	51/215 (24)	0.6 (0.4, 0.8)	0.005

a. Reflected as denominator in the columns.
b. Combined including 40 mg every other week (eow) and every week (ew).
c. P values based on Z score.
Note: The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 67 of the March 30, 2012 sBLA Resubmission.)

[2]Adalimumab Risk of Hospitalization and Colectomy R&D/12/280 submitted with the March 30, 2012 sBLA Resubmission.

Table 10: Exploratory Analysis #7b: Poisson Regression Analysis of All-Cause, UC and UC- or Drug-Related Hospitalizations (Hospitalization Analysis Set)

	E/PYs at Risk[a] (%)		
Outcome	ADA 160/80/40[b] N = 471	Placebo N = 468	*P* value[c]
All-cause hospitalization	83/401 (21)	69/224 (31)	0.0151
UC-related hospitalization	54/401 (13)	57/224 (25)	0.0008
UC- or drug-related hospitalization	63/401 (16)	61/224 (27)	0.0023

a. Reflected as denominator in the columns.
b. Combined including 40 mg eow and ew.
c. P values based on Poisson regression with time offset.
Note: Numbers in parentheses represent the number of hospitalizations on an annualized basis. The Hospitalization Analysis Set includes subjects in the IAS-E Analysis Set minus adalimumab 80/40 mg subjects in Study M06-826.
(Table above taken from Page 68 of the March 30, 2012 sBLA Resubmission.)

The FDA Clinical Reviewer concluded that the analyses are post hoc and do not alleviate concerns regarding the results of the pre-specified analyses.

An Information Request was sent to the Applicant to address the additional concerns about pooling of data across studies and the selective exclusion/inclusion of portions of the ITT population. The Applicant responded to this request and provided analyses of hospitalization data for each study and treatment arm separately; this data is summarized in the following table.

Table 11 : Exploratory Analysis 7 (Response to RFI)

Analysis Set Outcome	ADA 80/40 *P* value vs. Placebo	ADA 160/80 *P* value vs. Placebo
Study M06-826 ITT-E Safety Analysis Set		
All-cause hospitalization	0.117	0.046
UC-related hospitalization	0.038	0.012
Study M06-826 ITT-A3 Safety Analysis Set		
All-cause hospitalization	0.570	0.442
UC-related hospitalization	0.392	0.205
Study M06-827 ITT Safety Analysis Set		
All-cause hospitalization	n/a	0.271
UC-related hospitalization	n/a	0.060

Source: July 24, 2012 Response to the June 19, 2012 Clinical Information Request.

The all cause hospitalizations are a more robust measure of efficacy than UC-related hospitalizations which are un-adjudicated. In the analysis of individual studies the nominal p-values no longer suggest that the risk of hospitalization is lower with Humira. The ITT-E analysis set is exploratory by itself and an exploratory look at data in this set is even more difficult to interpret.

Exploratory Analysis #8 (Applicant): Partial Mayo Score Before and After Dose Escalation in Study 223

Exploratory Analysis #8 is summarized in the tables below.[3] This analysis is directly related to the CR Letter concern that the appropriate adalimumab dose for the pivotal efficacy trials may not have been selected .It is possible that the modest clinical remission rates observed in Studies 826 and 827 may be a reflection of an inadequate dose. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Study 223 allowed patients to escalate their dose from EOW to EW at Week 12 (if they entered from a blinded cohort) or at Week 2 (if they entered from an open label cohort) if they are inadequate responders or experience a disease flare (both defined based on specific partial Mayo Score and change in partial Mayo Score).

Of the total of 498 patients, 116 entered on 40 mg EW dosing from a previous study, 339 entered on 40 mg EOW dosing and did not dose escalate in Study 223, and 43 patients dose escalated from 40 mg EOW to 40 mg EW in Study 223.

Of the 43 patients that dose escalated, the number (percentage) of patients who dose escalated by week is shown in the table below:

Table 12: Number (Percentage) of Patients who Dose Escalated by Week (Study 223)

Week*	0	2	4	8	12	24	36	48	60	72	84	96
Number (%) of Patients Who Dose Escalated	0	2 (0.4%)	7 (1.4%)	8 (1.6%)	0	11 (2.2%)	5 (1.0%)	4 (0.8%)	4 (0.8%)	2 (0.4%)	0	0

*Partial Mayo Score Assessments were scheduled to occur on all these weeks.
(Table above summarized from Page 270 of the Study 223 Interim CSR dated March 13, 2012.)

Partial Mayo scores among subjects who switched from EOW dosing to EW dosing are shown in the table below.

[3] The analysis of dose escalation in Study 223 was submitted by the Applicant as part of the Study 223 Interim Clinical Study Report.

Table 13: Partial Mayo Score Before and After Dose Escalation, As Observed (ITT-1 Analysis Set)

	Adalimumab 40 mg eow/ew, N = 498		
Measurement Time Points	n	Mean ± SD[a]	Median[a]
Last partial Mayo score on adalimumab eow	43	6.0 ± 1.93	6.0
Last partial Mayo score on adalimumab ew	39	3.3 ± 2.23	3.0
Change	39	–2.6 ± 2.45	–3.0

eow = every other week; ew = every week; ITT = intent-to-treat
a. Mean and median scores calculated based on last available Mayo score while on eow dosing and on ew dosing.
Four subjects did not have a post-Baseline partial Mayo score available while on ew dosing due to the data cut-off of 31 December 2009.
Note: Summary includes only subjects who switched from eow to ew during this study.
(Table above taken from Page 119 of the Study 223 Interim Clinical Study Report dated March 13, 2012.)

The Clinical Reviewer noted that Partial Mayo scores among subjects who switched from EOW dosing to EW dosing decreased by 50% (from last EOW = 6.0 to last EW value = 3.0). However, the FDA Clinical Reviewer concluded that these data have limited informational value regarding added efficacy of a higher dose because there was no randomization to EOW or EW, the analysis was not pre-specified, and the underlying study was open-label.

7 Review of Safety (Additional Analyses submitted in Response to CR Letter)

7.1 Exploratory Analyses Overview

It is important to point out that the “integrated risk-benefit analysis" (using quantitative and exploratory analyses condensing complex data into one metric) the sponsor presents is very different from the benefit-risk assessment that supports FDA regulatory decisions. Our assessment is much broader than what is captured by these analyses and incorporates a wider range of factors, such as disease severity and patients' medical need, in addition to the extensive body of evidence on the drug's efficacy and safety. It also requires our scientific and clinical judgment about these factors and their importance. Because of this, as well as some specific limitations that will presented in section 7.2 this reviewer believes that that the Net Efficacy Analysis adjusted for Risk (NEAR) analysis and other combined metrics are not helpful as part of FDA’s benefit-risk assessment for Humira.

It should be noted that the discussion and presentation of Exploratory Analyses #9, #10, #11, and #12 shown below were provided by LaRee Tracy (Safety Statistics Team Leader) and Bradley McEvoy (Safety Statistics Reviewer) in preparation of the Advisory Committee Briefing Document. The safety statistics team was consulted after this reviewer had identified serious concerns with the combined safety-efficacy assessment the sponsor was proposing.

7.2 Exploratory Analyses in Detail

Exploratory Analysis #9 (Applicant): Serious Adverse Event (SAE)-Adjusted Days in Remission

The Applicant performed an exploratory analysis adjusting the days of clinical remission for days of serious adverse events (SAEs) leading to treatment discontinuation in Study 827. In this analysis, the mean days of SAEs leading to treatment discontinuation was subtracted from days of clinical remission. Despite the mean duration of SAEs being similar between the Humira 180/60 and placebo groups (4.11 and 4.64 days, respectively), the difference in SAE-adjusted days in clinical remission was statistically significantly different between groups. This difference is driven by the large difference in days of clinical remission (85.32 vs. 52.87 days in the Humira and placebo groups, respectively; p-value < 0.001). Therefore, it is unclear what additional information the SAE-adjusted analysis of days of clinical remission provides beyond what can be inferred from the analysis that only considered days of clinical remission. Furthermore, the clinical meaningfulness of this analysis is unclear given the pooling of all SAE time without accounting for type of event and the timing of the event in relation to clinical remission, if remission occurred.

Exploratory Analysis #10 (Applicant): Number of Patients who Discontinued Due to Adverse Events Relative to Number of Patients in Remission at Weeks 8 and 52

The Applicant conducted an exploratory analysis of Study 827 comparing the proportion of patients who achieved clinical remission at both Weeks 8 and 52 between treatment groups relative to those that had any AE that led to treatment discontinuation. For the individual endpoints, the ADA group had more subjects in clinical remission at both Weeks 8 and 52 (21 vs. 10, ADA and placebo respectively; Fisher p-value = 0.062) and fewer patients who discontinued due to an AE (22 vs. 30, ADA and placebo respectively; Fisher p-value=0.244). From these frequencies, the Applicant estimates that for every placebo subject who achieved clinical remission at both week 8 and week 52, 3.0 placebo subjects discontinued due to AEs; for ADA, the ratio is 1.0. The clinical meaningfulness of the ratios is unclear. This approach lumps together all AEs that led

to treatment discontinuation and therefore lacks in specificity of AE. This approach of lumping events can obscure imbalances between treatment groups for individual AEs.

The Applicant included a summary risk benefit measure, which is the ratio of the by-treatment risk to benefit ratios (Table 14). Specifically, the ratio of risk of discontinuing treatment due to AE to clinical remission in the placebo and ADA group is 30/10 (3.0) and 22/21 (1.0), respectively. The Applicant interprets this ratio as "placebo subjects are three times more likely to experience an AE leading to discontinuation than ADA subjects for the same level of clinical efficacy (measured by achieving clinical remission at Week 8 and Week 52)". The interpretation of this ratio of ratios is problematic for the following reasons: 1) the proportion of clinical efficacy differs between treatment groups, 2) this analysis does not fix the level of clinical efficacy in the estimation, and 3) this analysis assumes a one-to-one exchangeability for the efficacy and safety outcomes.

These same issues apply to the Applicant's risk benefit ratio obtained for subjects who discontinued treatment prematurely relative to the number of subjects in clinical remission at week 8 and clinical response at week 52 (results not presented).

Table 14: Number of Subjects who Discontinued Due to AEs Relative to the Number of subjects in Clinical Remission at Week 8 and Week 52 During the DB Period: Adalimumab Versus Placebo (Study M06-827 ITT Analysis Set; NRI)

	Placebo N = 246	ADA N = 248	*P* value
Subjects who discontinued due to AEs	30	22	
Subjects in clinical remission at Weeks 8 and 52	10	21	
Benefit/risk ratio (95% CI)	3.0 [1.5, 6.2]	1.0 [0.6, 1.9]	0.027

(Adapted from Applicant's Table 14 in resubmission)

Exploratory Analysis #11 (Applicant): Net Efficacy Adjusted Risk (NEAR) Analysis

The Applicant conducted an exploratory analysis combining clinical efficacy and safety into a single estimate. Their approach redefined the efficacy endpoint by only considering subjects with the efficacy response who also did not experience a particular safety event (i.e. a specific safety event-free treatment success). The odds of experiencing a safety event-free treatment success in the ADA group were then compared to the odds in the placebo group. The Applicant referred to this analysis as the Net Efficacy Adjusted for Risk (NEAR), which is discussed in a paper by Boada and colleagues[4,5]. The Applicant interprets a NEAR OR larger than one as a benefit-risk

[4] Boada JN, Boada C, García-Saíz M, et al. Net Efficacy Adjusted for Risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3580).

ratio in favor of ADA compared to placebo. Using pooled data from the placebo and ADA 160/80/40 mg group from Studies 826 and 827 (IAS-E analysis set), NEAR ORs were calculated for clinical response per Full Mayo (FM) and Partial Mayo (PM) score at Week 8 for the following two safety events: serious infections, and SAEs (which included serious infections).

Beyond issues raised previously about lumping together various safety endpoints and performing a pooled analysis, the ability of this NEAR analysis to quantify benefit-risk in a clinically meaningful way is highly questionable. The limitations of this approach are threefold. First, this approach implicitly assumes that the clinical benefit of having a clinical response is of equal importance/weight as experiencing a specific safety event. Such an assumption was not justified by the Applicant and is likely inappropriate due to the varying degree of safety events considered. The implication of this one-to-one exchange of efficacy for safety is illustrated by considering two hypothetical examples. In the first example, suppose that one ADA randomized study patient died. Using the NEAR approach, the estimated NEAR OR would differ minimally from the estimated OR from an analysis of only efficacy ignoring the potential safety concerns. In the second example, consider the week 8 remission analysis (per FM) which has 180/468 responses in the placebo group and 241/471 in the ADA group. Suppose there were 61 SAEs all occurring in the ADA group and they all occurred in patients that had a clinical response. In this case, the number of SAE-free treatment successes in the ADA group is 180/471 compared to 180/468 for placebo. In this extreme scenario (which has an alarming safety signal), per this approach and the Applicant's interpretation, the NEAR OR would be below one suggesting ADA has an unfavorable benefit-risk ratio; however, if there were 60 (or fewer) SAEs (still a large signal), the ADA group would have a favorable benefit-risk ratio. These examples suggest incongruence between the proposed quantification of benefit-risk (based on an adapted version of the NEAR) to how clinical benefit is considered along with risk.

A second limitation is that the comparison only contrasts the favorable aspects of benefit-risk, i.e. the numerator value is based on patients with clinical benefit and who did not experience the specific safety event of interest. Other aspects of benefit-risk that can be obtained from the cross-classification of the efficacy response and safety event, such as the proportion of patients that *did not* have a clinical response (e.g. no

[5] The NEAR approach described in the publication is considered flawed. By obtaining expected counts from the marginal event counts, one is implicitly assuming that the efficacy and safety endpoints are independent. Such an assumption is incorrect and was not discussed in the source article. Further, as a consequence of their approach, if group A has a greater percentage of patients with a positive efficacy endpoint and fewer AEs compared to group B, with probability 1 the odds of treatment group A will be larger than the odds for group B (i.e., the OR>1).

In addition, the Applicant's NEAR analysis differs from the approach described in the paper by Boada et al (2008). The difference is that the Applicant uses the observed number of subject that had an AE-free treatment success, whereas the source publication uses the expected numbers based on the marginal event counts within treatment groups.

remission) but *did* have an AE that led to treatment discontinuation, are not presented in the Applicant's NEAR analysis.

A third limitation is that the comparison only considers short-term efficacy with short-term risk. The problem with this is that short-term efficacy assessment is not done without also considering long-term risk when one assesses the overall risk benefit of a product. The failure of the analysis to incorporate temporal considerations, in addition to the above points, is sufficient reason to question the results from this analysis.

Exploratory Analysis #12 (Applicant): Number Needed to Harm (NNH) Analysis

The number needed to harm (NNH) corresponds to the number of patients needed to treat with Humira compared to placebo to result in one adverse event (SAE, AE leading to discontinuation, serious infections and malignancies). Estimates were derived by taking the inverse of the risk difference (1/difference of proportions) based on pooled data from the UC studies or from combined data from the UC and CD studies. Several point estimates were provided by the sponsor; however, it is unclear how clinically meaningful these values are without inclusion of confidence intervals, considering estimates when including data on all Humira exposures (not just on exposure to the Humira 160/80 treatment group) and understanding the type of events included (e.g. category of AEs leading to treatment discontinuation lacks in specificity of event).

The table below provides estimates of the NNH based on combined data from the two UC studies (826 and 827) using data collected up to 52 weeks. Two estimates are provided; one based on the inverse of the difference in proportion of events between placebo and the Humira 180/60 group and the second between placebo and all Humira. In addition, 95% CI (based on asymptotic method) are included to provide a measure of variability around the NNH estimates. The proportion of all SAEs in the placebo and Humira 160/80 groups are 10.1% and 8.3% respectively resulting NNH of -55 (1/(0.083-0.101)) with a 95% CI (-18, 53). This suggests a lower risk of SAE (when holding all other outcomes constant) in the Humira group. Also, note that the confidence intervals around several estimates presented in the table include infinity suggesting that the possibility of no difference between regimens cannot be ruled out.

Table 15: NNH Values based on Data for 0-52 Weeks (UC Studies 826 and 827 Combined)

Event	Placebo (n=483)	Humira 160/80 (n=480)	All Humira (n=1010)
All SAEs	49 (10.1)	40 (8.3)	254 (25.1)
NNH (95% CI)		*-56 (-18, 53)*	*7 (5, 9)*
AE leading to Treatment D/C	46 (9.5)	36 (7.5)	206 (20.4)
NNH (95% CI)		*-49 (-18, 65)*	*9 (7, 14)*
Serious Infections	8 (1.7)	4 (0.8)	58 (5.7)
NNH (95% CI)		*-122 (-40, 148)*	*24 (17, 47)*
Malignancy (excl. NMSC)	1 (0.2)	1 (0.2)	15 (1.5)
NNH (95% CI)		*77280 (-102, 102)*	*78 (44, 423)*

Event counts based on those reported in Sponsor's Table 26 of AC Briefing Document, NNH estimates based on inverse of the risk difference (Humira-placebo), a negative NNH suggests decreased risk in Humira group relative to placebo, a positive value suggests increased risk in Humira relative to placebo

The sponsor also provided estimates on the number needed to treat (NNT) for clinical remission, response, mucosal healing and IBDQ response. The issues raised above also apply to these analyses of NNT along with limitations in pooling data for efficacy assessments.

7.3 Updated Major Safety Results

For an in-depth-safety review please refer to the 1st cycle review. Since the initial submission no new safety signals have become apparent. However, the total number of deaths has increased from 1 to 4 since the 1st cycle review.

No deaths were reported in Studies 826 or 827. There were 4 deaths (0.2 events/100 PYs) reported in the open-label portion of the UC clinical program through 15 April 2012. Two deaths were treatment-emergent, and 2 deaths were post-treatment (defined as greater than 70 days after last adalimumab dose).

Treatment emergent:

In one 34-year-old male patient who apparently had sepsis the pathologist concluded that the patient died of shock associated with bilateral adrenal hemorrhage secondary to an infectious process whose etiology could not be determined from the autopsy.This death was also reviewed by the Clinical reviewer who prepared the review for this initial submission.

A 47-year-old female the findings on autopsy included acute pulmonary edema (in the sponsor's document typed as "acute pulmonary emphysema" but given the context "acute pulmonary edema" must have been meant), general atherosclerosis including coronary arteries, hypertrophy and dilation of the right ventricle.

Post-treatment

A 73-year-old female with a previous diagnosis of lymphoma (considered resolved prior to death) had an event of cardiopulmonary arrest and died 982 days after her last dose of adalimumab. No autopsy was performed.

A 46-year-old female died with cause of death listed as pulmonary embolism on Day 1135, 72 days after the last dose of adalimumab.The patient suffered from morbid obesity and longstanding UC. No autopsy was performed.

7.4. Immunogenicity

For details please see 1st cycle clinical review and Clinical Pharmacology Review

For the current application the assessment of immunogenicity was not adequate because most samples were not appropriately evaluated due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement, and therefore, whether Humira actually offers immunogenicity advantages remains unknown.

8 Postmarket Experience

See 1st Cycle Clinical Review

Appendices

9.1 Complete Response Letter

BLA 125057/232

COMPLETE RESPONSE

November 21, 2011

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

We acknowledge receipt of your amendments dated March 25, 2011, April 28, 2011, May 24, 2011, May 27, 2011, June 06, 2011, July 25, 2011, July 27, 2011, September 21, 2011, September 29, 2011, October 07, 2011, and October 12, 2011.

This "Prior Approval" efficacy supplement to your biologics license application proposes to add the indication of reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining

induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are two-fold.

First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

Second, we are concerned that you may not have adequately selected an appropriate adalimumab dose for your pivotal efficacy trials. We note the modest improvement in clinical remission rates reported in both trials (treatment differences relative to placebo in clinical remission at Week 8 of 9.3% and 7.2% in Studies M06-826 and M06-827, respectively), and the treatment difference relative to placebo in sustained clinical remission (at both Weeks 8 and 52) of 4.4% in Study M06-827.

To address these concerns, we will need to seek expert advice at a future meeting of the Gastrointestinal Drugs Advisory Committee.

LABELING

2. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

3. During a recent inspection of the [redacted] (b) (4) facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Although these are not approvability issues at this time, we request that you respond to the following comments in your re-submission:

IMMUNOGENICITY

1. The immunogenicity assay was not adequate because the original and new immunogenicity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. Therefore, there is a need to develop an assay with improved drug tolerance.

To address this issue, you should develop, qualify and implement an improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patient samples collected from clinical studies should be banked under appropriate storage conditions.

2. The immunogenicity profile for adalimumab has not been adequately assessed.

   Utilizing a validated AAA assay as described in Item #1 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay.

STATISTICAL

3. STUDY M06-826

   a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in

the subgroup analysis based on CRP < 10.0 mg/L vs. CRP ≥10.0 mg/L (13.4% vs. -4.5%).

4. STUDY M06-827

   a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

   b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% vs. 12.1%.

   c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
    - Present tabulations of the new safety data combined with the initial data.
    - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on "Formal Meetings Between FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

/ ANDREW E. MULBERG /
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Division Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

4 Pages of Draft Labeling have been Withheld in Full as b4 (TS/CCI) immediately follwoing this page.



9.3 Advisory Committee Meeting

The following is an internal report which has not been reviewed. A verbatim transcript will be available and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm291609.htm
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Center for Drug Evaluation and Research met on August 28, 2012 from 8 a.m. to 3:14 p.m. at the DoubleTree by Hilton Hotel Washington DC-Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were screened and cleared for conflict of interest, and provided copies of the background material from the FDA. The meeting was called to order by Atul Kumar, M.D. (Acting Committee Chairperson); the conflict of interest statement was read into the record by Cindy Hong, Pharm.D. (Designated Federal Officer). There were approximately 150 persons in attendance. There were three (3) speakers for the Open Public Hearing session.

Issue: The committee discussed the results from clinical trials of supplemental biologics license application (sBLA) 125057/232, for Humira (adalimumab), by Abbott Laboratories, for the proposed indication (use) for reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Attendance:
Gastrointestinal Drugs Advisory Committee Members Present (Voting):
Garnet Anderson, Ph.D., Elizabeth Bell-Perkins (Consumer Representative), M.P.H., Atul Kumar, M.D. (Acting Chairperson), Marc Wishingrad, M.D.

Temporary Members (Voting): Jeffrey Barrett, Ph.D., Matthew Chandler, M.D., Marilyn Eichner (Patient Representative), Thomas Fleming, Ph.D., Ivan Fuss, M.D., Jason Hou, M.D., Andelka LoSavio, M.D., Lilani Perera, M.D., Michael Rice, M.D., Richard Rood, M.D., Harohalli Shashidhar, M.D., Amandeep Shergill, M.D., Xinjun Cindy Zhu, M.D.

Industry Representative to the Gastrointestinal Drugs Advisory Committee (Non-Voting):
Helmut H. Albrecht, M.D., M.S., FFPM

FDA Participants (Non-Voting):
Klaus Gottlieb, M.D., M.B.A., M.S., R.A.C., Nitin Mehrotra, Ph.D., Andrew Mulberg, M.D., F.A.A.P., C.P.I., Anil Rajpal, M.D., M.P.H., Mike Welch, Ph.D.

Gastrointestinal Drugs Advisory Committee Members Not Present:
Ronald Fogel, M.D., Amy Foxx-Orenstein, D.O., Richard Grand, M.D., Gagan Sood, M.D., Steven Solga, M.D.

Designated Federal Officer:
Cindy Hong, Pharm.D.

Open Public Hearing Speakers:
Kimberly Frederick, Crohn's & Colitis Foundation of America
Stacey Kane
Leyla Ghazi, University of Maryland Medical Center

The agenda was as follows:

Call to Order Introduction of Committee	**Atul Kumar, M.D.** Acting Committee Chairperson, GIDAC
Conflict of Interest Statement	**Cindy Hong, Pharm.D.** Designated Federal Officer, GIDAC
Opening Remarks	**Andrew E. Mulberg, M.D., F.A.A.P.** Deputy Director, Division of Gastroenterology and Inborn Error Products (DGIEP), Office of Drug Evaluation (ODE) III, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER),

	Food and Drug Administration (FDA)
Sponsor Presentations	**Abbott Laboratories, Inc.**
Introduction	**John Medich, Ph.D.** Division Vice President, Immunology, Abbott Laboratories
Disease Background	**Subrata Ghosh, MBBS., M.D., FRCPC, FRCP, FRCPE** Professor and Chair of the Department of Medicine University of Calgary Alberta, Canada
Efficacy	**Roopal Thakkar, M.D.** Project Director, Immunology Abbott Laboratories
Safety	**Andrea Best, D.O, M.P.H** Senior Medical Director, Immunology Product Safety Abbott Laboratories
Benefit/Risk Assessment	**Roopal Thakkar, M.D.**
Clinical Perspective	**William Sandborn, M.D.** Chief, Division of Gastroenterology University of California San Diego School of Medicine
Conclusion	**John Medich, Ph.D.**
Clarifying Questions to the Presenters	
FDA Presentations	
Clinical/Statistics	**Klaus Gottlieb, M.D., M.B.A., M.S.** Medical Officer, DGIEP, ODE III, OND, CDER, FDA
Clinical Pharmacology	**Nitin Mehrotra, Ph.D.** Clinical Pharmacology Reviewer, Office of Clinical Pharmacology, CDER, FDA

Summary — **Anil Rajpal, M.D., M.P.H.**
Medical Team Leader,
DGIEP, ODE III, OND, CDER, FDA

Clarifying Questions to the Presenters

Open Public Hearing

Questions to the Committee and Committee Discussion

Adjournment

Questions to the Committee:

1. Dose Selection:

   VOTE: Based on the exposure-response data and observed treatment effect presented, has the optimal Humira dose for treatment of moderately to severely active ulcerative colitis (UC) been adequately established? Please comment on the need for further dose exploration.

   YES: 3 **NO: 14** **ABSTAIN: 0**

Those voting "Yes" commented that while the dose studied is clinically effective for anti-TNF naïve patients, an optimal dose has not been fully established. It was also noted that while the current dosing schedule was clinically effective in some patients, others required a higher dose of 40mg every week. The committee noted that the sponsor had requested for the product label to allow a higher dose in non responders. Such variable dosing is likely to minimize risk in responders, while allowing others to receive higher doses for clinical effectiveness. There were also comments that a post marketing dose ranging study was required.

Those who voted "No" noted that the optimal dosing for this drug has not been fully explored given FDA's concentration response analysis. Although the dosage used demonstrated clinical efficacy, the therapeutic effect continued to rise and did not plateau for the doses studied. It was commented that a higher dose study may have facilitated a better response; hence a post approval dose response study is needed.

2. Efficacy Analysis (Studies 826 and 827):

   (a) **DISCUSSION:** Please discuss the factors that you consider in defining the term "**clinically meaningful benefit**" in patients with moderately to severely active UC.

Reference ID: 3196365

Panel members expressed a range of opinions on this issue. Statistically significant clinical efficacy alone does not imply "clinically meaningful benefit". Such results require interpretation within the context of disease burden, safety, availability of other therapies and the therapeutic pipeline. Hence, a certain magnitude of difference between placebo and treatment groups assessed either by way of a delta or odds ratio or relative risk cannot alone determine "clinically meaningful benefit". Safety of Humira was of particular concern to some panel members; and in particular, the long term safety of the drug had not been fully evaluated. The impact of the disease on the quality of life and the need for alternative therapies were noteworthy concerns in other opinions. The steroid sparing effects or colectomy avoiding attributes of the drug were of significant importance. Patient age, duration of disease, length of therapy, and convenience of dosing were also mentioned as factors to consider. In summary, "clinically meaningful" is a subjective measure, and apart from risk benefit analysis, is dependent on patient (&physician) preferences and their risk tolerance. Within the advisory committee there was variance in the comfort level with the risk-benefit trade off in the context of clinical effectiveness. While there was unanimity regarding the lack of long term safety record for this specific indication, given the track record of this drug for other medical conditions, most members were willing to accept the safety concerns, and endorse it despite its marginal effectiveness for UC.

(b) Clinical Remission at Week 8:
VOTE: Do the observed treatment differences (Humira 160/80/40 versus placebo) in the proportion of patients that had clinical remission at Week 8 of **9.3%** (95% CI: 0.8%, 17.9%) (Study 826) and **7.2%** (95% CI: 1.3%, 13.2%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

YES: 15 **NO: 1** **ABSTAIN: 1**

Those voting "Yes" commented about unmet need, compliance & convenience issues, which favored having adalimumab as a treatment option. The study did show statistical significance as compared to placebo, at week 8, albeit the differences being marginal. One member noted the long record of use of this drug and of the class of drugs. Several noted that currently given few treatment choices, adalimumab would be another option, especially for difficult to treat patients. Committee members hence endorsed Humira voting that it resulted in clinically meaningful benefit. Even the marginal benefit was acceptable given the high disease burden with regards to its impact on quality of life.

The member who voted "No" commented that although Week 8 results are statistically significant, it failed to meet the member's assessment of clinically meaningful because of inadequate information on durability of response and safety. It was also noted that the data suggest that it is best to use adalimumab as an alternative to Remicade as opposed to salvage therapy following Remicade. Data thus far suggests that benefits following Remicade are modest.

The member who voted "Abstain" commented that there wasn't enough information to provide a reliable answer and also commented that the answer could be "yes" if it could be determined that there weren't substantive safety issues, that the drug effect is durable, evidence was present to indicate adalimumab is effective in patients not adequately

controlled by existing therapies, and that such data were reliable. However, the probability of "No" appeared much more likely then a "Yes," hence the abstention.

(c) Clinical Remission at Week 52:

(i) **VOTE:** Does having clinical remission at Week 52 represent a clinically meaningful endpoint? (please explain your vote)

YES: 16 NO: 1 ABSTAIN: 0

The members who voted "Yes" commented that Week 52 as a marker for durability of effect is a meaningful endpoint. It was also commented that remission is at the top of the list of what patients want to see.

The member who voted "No" commented that interpreting the question as related to the practicality of obtaining long-term data reliably, while desirable, is logistically challenging. To successfully conduct a trial of such a long duration given the likelihood of significant drop out rates and loss to follow up, without adversely impacting reliable and meaningful results is difficult.

(ii) **VOTE:** Does the observed treatment difference in the proportion of patients that had clinical remission at Week 52 of **8.8%** (95% CI: 2.9%, 14.8%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

YES: 15 NO: 1 ABSTAIN: 1

The members who voted "Yes" commented that the decision was made mainly on reasons discussed previously and due to durability of sustained response. One member noted that this is a more significant finding, showing consistency of continued exposure. Most members agreed that the result is clinically relevant at Week 52.

The member who voted "No" commented that the data does not represent clinically meaningful benefit and is not confident in the interpretation of the data at Week 52. It was also noted that the durability issue is not answered because it is a cross sectional look.

The member who voted "Abstain" noted that the decision was arrived for the same reasons as Question 2b. It was noted that the vote could be "Yes" if the agent was truly safe and if we knew the value of 8.8% was real and a vote could be "No" because we can't conclude there isn't a real risk for malignancy and serious infection.

(d) Clinical Remission at Both Weeks 8 and 52:
VOTE: Does the observed treatment difference in the proportion of patients that had clinical remission at both Weeks 8 and 52 of **4.4%** (95% CI: 0.1%, 9.0%) (Study 827) represent a clinically meaningful benefit? (please explain your vote)

YES: 10 **NO: 6** **ABSTAIN: 1**

Members voting "Yes" commented that the magnitude of effect is disappointing, but does seem meaningful given the subset of patients who are difficult to treat. Some members expressed concerns regarding missing data for long term safety, but noted that benefits were seen.

The members who voted "No" commented that because of the unknown about safety and missing data, the answer could not be a Yes. It was also noted that the value of 4.4% for durability is very low for an agent that has the risks that are known.

One member voted "Abstain" for reasons that the magnitude of effect is disappointing but a rigorous endpoint and that the 4.4% is difficult to interpret when explaining the trial results to a patient.

3. Additional Pre-Approval Studies:

VOTE: Are there additional efficacy studies that should be conducted prior to approving Humira for moderately to severely active UC? (please explain your vote)

YES: 3 **NO: 13** **ABSTAIN: 1**

Those who voted "Yes" commented that we need to further explore efficacy, safety, and dose. One member commented on the need for randomization trials involving patients with inadequate response or intolerance to existing therapy.

Those who voted "No" commented that there are studies needed, but not for approval of the medication and the approval should not be held up for the proposed indication. Most of these members expressed the need for post approval dosing and safety trials.

One member abstained from voting due to unclear phrasing and noted the contingency of approval should not be dependent on efficacy studies, but the medication should be tailored to
specific patient populations and more studies are necessary, especially looking at the safety profile.

One member who had originally voted "Yes," subsequently noted during the explanation of the vote that she wanted to vote "No" and did not feel there is a need for additional studies before approval, but does want to see post approval studies and sub population response to adalimumab. The vote count above records her vote as "Yes".

4. Benefit-Risk Considerations:

VOTE: Do the expected benefits outweigh the known and potential risks of Humira for the treatment of patients with moderately to severely active UC based on currently available data? If YES, specify whether your answer is limited to particular population(s) defined by level of disease severity or inadequate response/intolerance to prior therapies. (please explain your vote)

YES: 15 NO: 2 ABSTAIN: 0

Those who voted "Yes" commented that benefits outweigh the risks in various populations, given earlier discussions. The efficacy extended to patients intolerant to other anti-TNF therapies, anti-TNF naïve patients, those not responding to other conventional therapies, and populations with moderately to severely active disease. A few members noted that there is not enough data at this point to limit to certain populations.

Those who voted "No" commented that there are modest effects, but also uncertain durability and uncertain dose. One member also noted the lack of confidence in week 52 data.

5. Post-Approval Studies:

DISCUSSION: If you believe this product should be approved for moderately to severely active UC, are there any additional studies you would recommend post-approval?

The panel commented on the need to explore higher doses and since baseline efficacy has already been established, there is a need to maximize efficacy. It was also noted that in addition to the need for exploration of drug dosage issues, the mechanism of action of the drug needs to be looked at more in depth.

The panel also wanted to see studies which will explore when to introduce a drug of this class, who is likely to benefit, and reasons for loss of response (i.e. immunogenicity or dose related). There were comments on the need for studies in young adults/teenage population especially in terms of safety and also gender specific responses.

The need for studies evaluating the correlation of serum trough levels with clinical effectiveness was noted. Also, it was pointed out that anti-adalimumab antibody measurements were not standardized and clinically available. The sponsor commented that they were committed to developing an improved immunogenicity assay and to have it made available shortly.

(Please see official transcript for details.)

The meeting adjourned at approximately 3:14 p.m.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
09/27/2012

ANIL K RAJPAL
09/28/2012
I concur with Dr. Gottlieb.

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125057/232
Priority or Standard	Standard
Submit Date(s)	25 January 2011
Received Date(s)	25 January 2011
PDUFA Goal Date	25 November 2011
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer	Aisha Peterson Johnson, MD, MPH, MBA 10/21/2011
Team Leader	Anil Rajpal, MD Anil Rajpal, MD 10/21/11
Review Completion Date	October 21, 2011
Established Name	Adalimumab
Trade Name	Humira
Therapeutic Class	TNF Antagonist
Applicant	Abbot Laboratories
Formulation(s)	40 mg/0.8mL in prefilled syringe or pen
Dosing Regimen	160 mg SC at Week 0, 80 mg SC at Week 2, followed by 40 mg eow
Indication(s)	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis
Intended Population(s)	Adults with moderately to severely active ulcerative colitis who have failed conventional therapy

Template Version: March 6, 2009

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	125057/232
Priority or Standard	Standard
Submit Date(s)	25 January 2011
Received Date(s)	25 January 2011
PDUFA Goal Date	25 November 2011
Division / Office	Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)/ Office of Drug Evaluation III
Reviewer Name(s)	Aisha Peterson Johnson MD, MPH, MBA
Review Completion Date	22 October 2011
Established Name	Adalimumab
Trade Name	Humira
Therapeutic Class	TNF Antagonist
Applicant	Abbot Laboratories
Formulation(s)	40 mg/0.8mL in prefilled syringe or pen
Dosing Regimen	160 mg SC at Week 0, 80 mg SC at Week 2, followed by 40 mg eow
Indication(s)	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis
Intended Population(s)	Adults with moderately to severely active ulcerative colitis who have failed conventional therapy

Template Version: March 6, 2009

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Reference ID: 3200370

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is the recommendation of this reviewer that a Complete Response action be taken regarding the current Humira supplemental BLA.

1.2 Risk Benefit Assessment

Review of the current Application reveals that the benefit of Humira for reducing signs and symptoms and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy does not outweigh the risks. Given the known serious risks associated with the use of Humira, the clinical benefit of Humira for the proposed indications has not been adequately demonstrated.

Studies 826 and 827 were submitted in support of the proposed induction and maintenance indications for this supplemental BLA. The primary efficacy endpoint of Study 826 was the proportion of subjects in clinical remission at Week 8; in addition, Study 826 included a number of ranked secondary endpoints assessed at Week 8. Study 827 had a ranked co-primary efficacy endpoint (the proportion of subjects in clinical remission at Week 8, followed by the proportion of subjects in clinical remission at Week 52); in addition, Study 827 included a number of ranked secondary endpoints assessed at Weeks 8 and/or 52 (the first-ranked secondary endpoint was the proportion of subjects in clinical remission at both Weeks 8 and 52). (In both studies, clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1.)

Induction of Clinical Remission (Studies 826 and 827):

The studies do not provide adequate evidence that Humira is efficacious for the proposed indications. Two dose groups of Humira (160/80/40 mg and 80/40 mg) were tested. There was no statistically significant difference between the low dose Humira group and placebo, p=0.833. For the 160/80/40 mg dose group, the treatment difference between Humira and placebo was low in both studies--9.3% in Study 826 and and 7.2% in Study 827. This reviewer believes that a treatment difference of less than 10% is likely not clinically meaningful and therefore it is not appropriate to approve Humira for the UC indications at this time given the known serious adverse events associated with the use of Humira. These known risks include malignancies, serious infections, serious allergic reactions, hepatitis B virus reactivation, new onset or exacerbation of demyelinating disease, new or worsening heart failure, and lupus-like syndrome.

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Robustness of Data in Study 826: In addition to the problem of a small treatment difference (9.3%) seen in Study 826, there is also the issue of a lack of robustness of the data. First, the p-value varies considerably based on which test of significance is used. Using the pre-specified test of significance, Chi-squared, the calculated p-value is 0.031. However, if Fisher's Exact Test (a more conservative analysis method than the Chi-squared approximation) is used, the p-value is 0.047. This value only borders on statistical significance. Second, the value of Fisher's Exact Test becomes greater than 0.05 if the remission status of one patient (0.8% change) in either treatment group changes. Specifically, if the status of one Humira patient changes from remitter to non-remitter or one patient in the placebo group changes from non-remitter to remitter, the value of Fisher's Exact Test changes to 0.068 and 0.075, respectively. Third, none of the secondary endpoints provided support for the results seen in the primary endpoint. Finally, the first of 12 ranked secondary endpoints (clinical response at Week 8) failed to show statistical significance. Because the endpoints are ranked, failure of the first endpoint to show statistical significance meant that no other endpoints can be investigated for statistical significance. These results do not support the primary endpoint results.

"Maintenance of Clinical Remission" / "Sustained Clinical Remission" (Study 827):

For the "maintenance of clinical remission" indication (Applicant's proposed label language), Study 827 was the only study submitted. However, this study was not designed to measure "maintenance of remission;" instead, Study 827 was designed to evaluate "sustained clinical remission." To support a claim of "maintenance of remission", patients in remission at Week 8 should have been re-randomized because without re-randomization, any effect of Humira on maintenance could be confounded with an effect on induction. (This point was communicated to the sponsor in a pre-submission advice letter about the statistical analysis plan of Study 827.) This reviewer believes that for a more robust demonstration of the activity of Humira for the maintenance of remission, the Applicant should perform an appropriately designed maintenance study.

"Sustained clinical remission" was defined as being in remission at both Weeks 8 and 52. The first-ranked secondary endpoint of Study 827 was the proportion of subjects that had "sustained clinical remission" using this definition, and was examined by this reviewer as the best reflection of whether Humira had efficacy for maintenance of remission. Only 8.5 % of Humira patients had "sustained clinical remission" compared with 4.1% of placebo patients (4.4% treatment difference). The statistical significance of this difference is borderline; p-value=0.047. This reviewer believes that this 4.4% treatment difference likely has very little clinical meaningfulness. This reviewer believes that exposing patients to a TNF blocker for 52 weeks to realize a 4.4% treatment difference is not appropriate given the known serious adverse events associated with the use of TNF blockers.

Cross-study Comparisons with Remicade:

For adult patients with moderately to severely active UC, there is currently a product on the market—Remicade. Remicade is also a TNF-blocker. Although there are limitations of cross-study comparisons, the results suggest that the magnitude of the treatment effect with Humira is lower than that with Remicade.

Induction of Clinical Remission: Remicade registration trials revealed an induction (Week 8) treatment difference (Remicade-placebo) of 24% (ACT 1) and 28% (ACT 2) with the 5 mg/kg dose (approved dose for UC). This is considerably higher than the treatment difference for induction seen with Humira in Studies 826 and 827, 9.3% and 7.2%, respectively. Remicade and Humira were studied in similar patient populations and the approval studies (for both products) used the same primary endpoint for induction of clinical remission (i.e., total Mayo score of ≤2 with no individual subscore >1 at Week 8).

"Maintenance of Clinical Remission" / "Sustained Clinical Remission": The treatment difference for the "sustained clinical remission" endpoint seen in the Remicade "maintenance study" (ACT 1) was 13%. This is considerably higher than the treatment difference for the "sustained clinical remission" endpoint seen with Humira in Study 827, 4.4%. However, it should be noted that the definition of "sustained clinical remission" differed between the Remicade study (ACT 1) and the Humira study (827). The Remicade study (ACT 1) defined "sustained clinical remission" as clinical remission at Weeks 8, 30, and 54; in contrast, the Humira study (827) defined "sustained clinical remission" as clinical remission at Weeks 8 and 52. [The definition of clinical remission was the same for both the Remicade study (ACT 1) and the Humira study (827); i.e., total Mayo score of ≤2 with no individual subscore >1].

Safety: Additionally, this reviewer believes that the safety profiles of Remicade and Humira are very similar. According to current Remicade labeling the incidence of infusion reactions was 20%. In Humira UC studies, the incidence of injection reactions was also 20%. The incidence of infections in Remicade-treated patients was 36%. In Humira UC studies, the incidence of infections Humira patients was 38% (maintenance set). There were no major safety differences noted between Remicade and Humira.

Immunogenicity: One issue associated with the use of Remicade (infliximab) is the development of anti-drug antibodies. The development of these Human Anti-Chimeric Antibodies (antibodies against infliximab) may lead to infusion reactions and/or reduced duration of efficacy. According to current Remicade labeling, the incidence of antibodies to infliximab was 10% in Crohn's disease patients and 36-51% in psoriasis patients over one year of treatment. Because Humira is humanized, it is hypothesized that there will be less development of anti-drug antibodies. According to current Humira labeling, approximately 5% of patients developed antibodies to adalimumab in adult rheumatoid arthritis studies. However, a recently published long-term cohort study

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of patients taking Humira reported that 28% (76/272) of patients developed anti-adalimumab antibodies over a three year period, with 67% of these occurring during the first 28 weeks of treatment.[1] Unfortunately, the assessment of immunogenicity in the current application was not adequate and therefore, whether Humira actually offers immunogenicity advantages remains unknown.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

N/A

1.4 Recommendations for Postmarket Requirements and Commitments

N/A

2 Introduction and Regulatory Background

2.1 Product Information

Trade Name:	Humira
Generic Name:	adalimumab
Therapeutic Class:	Anti-inflammatory
Formulation:	Delayed-release tablets containing 1.2 g mesalamine
Proposed indication:	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, only Remicade is FDA approved for the induction and maintenance of remission of moderately to severely active ulcerative colitis (UC) in adult patients who have failed or had an inadequate response to conventional therapy.

2.3 Availability of Proposed Active Ingredient in the United States

This product is currently licensed and marketed in the United States for other indications.

[1] Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg, PA, Lems WF, et al Development of Antidrug Antibodies Against Adalimumab and Association with Disease Activity and Treatment Failure During Long-term Follow-up. JAMA April 13, 2011 vol 305 no 14 p1460-1468

2.4 Important Safety Issues With Consideration to Related Drugs

An increased risk of serious infections and lymphoma is associated with TNF antagonist therapy. These risks are adequately reflected in current labeling with a black box warning.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1. Pre-submission Regulatory History, BLA 125057/232, s005

Date	Regulatory Action(s)
23 November 2010	Pre-sBLA Meeting ▪ Agency recommended a *post hoc* analysis of the remission endpoint. Specifically, the Agency recommended a definition of clinical remission of total Mayo score ≤2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability). This new definition of clinical remission is more in line with current Agency recommendations.
24 May 2010	The Agency provided comments and responses to Applicant questions regarding Study 827. ▪ **Agency advised Applicant that Study 827 was not designed to evaluate efficacy for maintenance of clinical remission. The Agency stated that the study was, instead, designed to evaluate remission and induction of sustained clinical remission.** ▪ **Agency advised that without re-randomization, any effect on maintenance would be confounded with an effect on induction.**
16 September 2008	Advice letter sent to Applicant regarding Statistical Analysis Plan for Study 826 with the following comments: ▪ If patients are unblinded after Week 8, then results from efficacy analyses beyond Week 8 should be considered exploratory. ▪ You need to justify how your gatekeeper procedure for ranked secondary endpoints controls for the family-wise error rate at the significance level of 0.05 (2-sided). ▪ Since no adjustments for multiplicity will be done for other non-ranked secondary endpoints, those analyses should be considered as exploratory. ▪ **Results from analysis of "time to" clinical response per partial Mayo** score up to Week 8 should also be considered as exploratory.
15 June 2006	Pre-IND/pre-Phase 3 Meeting ▪ Agency outlined risks associated with lack of Phase 2 program including risk that Week 8 is not optimal time point for induction endpoint. ▪ Agency expressed concern that the maintenance study design does not support indication because responders at Week 8 are allowed to continue in the study for assessment of remission at a later time point.

2.6 Other Relevant Background Information

Other than that discussed in other sections of this review, there is no other relevant background pertinent to the current review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well-organized and easily navigable.

The Division of Scientific Investigations (DSI) performed a single site investigation of Site 29080 in Toronto, Canada. The site enrolled 53 patients (approximately 10% of total patients) in Study 826.

DSI recommended that data from the inspected site can be used in support of the BLA.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all of the studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

3.3 Financial Disclosures

For studies 826, 827, and 223, the Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Financial disclosures were provided for 48 investigators involved in one or more of the studies submitted with the current Application. The Applicant's financial disclosure summary provided the amount of payments to each investigator (exclusive of money to conduct the study). The total amount of these payments was reported as >$25,000 or >$50,000. See Table 2 below for further details regarding financial disclosures.

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Financial disclosures below $25,000 were not reported. All disclosures were >$25,000 but less than $50,000 except for one (b) (4), (b) (6), a subinvestigator for (b) (4) in Wisconsin, disclosed an equity interest in Abbott common stock greater than $50,000.

Of the 576 patients enrolled in Study 826, 206 patients (36%) were enrolled in sites where the investigator and/or sub-investigator received payments from Abbot totaling at least $25,000 (other than payments for conducting the study). Of the 517 patients enrolled in Study 827, 118 patients (23%) were enrolled in sites where the investigator and/or sub-investigator received payments from Abbott totaling at least $25,000 (other than payments for conducting the study). Study 223 was ongoing and enrollment was not complete at the time that financial disclosure forms were submitted.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Applicant did not submit any new CMC information. The validated immunogenicity assay approved under the original BLA was used for evaluation of anti-adalimumab antibody (ADA) for this supplement. No CMC issues were identified and the supplement was recommended for approval from the CMC perspective.

4.2 Clinical Microbiology

No CMC changes have been proposed in the current submission that might affect the sterility of the product.

4.3 Preclinical Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this supplemental NDA.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

From Current Humira Labeling, Section 12.1 Mechanism of Action

> *Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.*
>
> *Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10-10M).*

4.4.2 Pharmacodynamics

Current Humira Label:

> *After treatment with HUMIRA, a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in*

patients with Crohn's disease. Serum level*s of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.*

For a description of the remission results for the Humira UC studies by baseline CRP level at baseline, see Section 6.1.4 below. In general, no statistically significant difference was in remission rate was seen in patients with baseline CRP ≥10 mg/dL.

4.4.3 Pharmacokinetics

Pharmacokinetic and immunogenicity data were collected in Study 827. See Table 3 for a list of the studies submitted in support of this Application.

The exposure-response relationship for clinical remission at Week 8 does not support the proposed dosing regimen (160/80/40 mg) for the induction phase. The proportion of patients in remission increases with increasing exposure to Humira and that exposure-response curve does not plateau. Further, using logistic regression, a statistically significant (p=0.0002) relationship was demonstrated between Humira Week 8 trough concentrations and the proportion of patients in remission at Week 8. These facts suggest that a higher dose may provide greater benefit for patients (i.e., a higher proportion of patients in remission at Week 8). No dosing regimens higher than 160/80/40 mg has been tested by the Applicant.

Due to a large number of dropouts, a robust exposure-response relationship could not be established for clinical remission at Week 52 (maintenance of remission).

For more information see the Clinical Pharmacology Review by Lin Zhou, PhD and Nitin **Mehrotra PhD (with FDA Commissioner's** Fellow Michael Bewernitz, PhD).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Clinical Trials Submitted in Support of the Current Application

Study	Primary Endpoint	Treatment Arms
M06-826	Induction of Clinical Remission (Week 8)	160/80/40* 80/40# Placebo
M06-827	Induction of Clinical Remission (Week 8)	160/80/40* Placebo
	Maintenance of Clinical Remission (Week 52)	**40 mg†** Placebo

M10-223*	Long-term maintenance of response, safety, tolerability	**40 mg‡**

*Adalimumab 160/80/40 SC EOW: 160 mg at Wk 0, 80 mg at Wk 2, and 40 mg at Wk 4 and every other wk
#Adalimumab 80/40 SC EOW: 80 mg at Wk 0, 40 mg at Wk 2 and every other wk
†Adalimumab 40 mg SC EOW: 40 mg every other wk
‡Adalimumab 40 mg SC EOW/EW: every other wk or every wk

5.2 Review Strategy

For this BLA submission, Studies 826 and 827 were reviewed in detail. Details of the study design and conduct are contained in Section 5. Study results are discussed in Sections 6 (efficacy) and 7 (safety). Study 223 safety results are included in the All Humira population of the safety section.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title
Study 826
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis

Study 827
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis

Study Centers
Study 826
This study was conducted in 80 centers in 12 countries. Participating countries included Austria, Belgium, Canada, Czech Republic, Germany, Hungary, Italy, the Netherlands, Poland, Slovakia, Sweden, and the United States.

Study 827
This study was conducted in 103 centers in 17 countries. Participating countries included Austria, Belgium, Denmark, France, Germany, Israel, Norway, Portugal, Spain, Switzerland, the Czech Republic, Hungary, Poland, Australia, and New Zealand.

Study Period
Study 826
13 November 2006 to 05 March 2010

Study 827
20 November 2006 to 02 March 2010

Study Objective
Study 826
The primary objective of this study was to assess the efficacy and safety of two dosing regimens of adalimumab for the induction of clinical remission in patients with moderately to severely active ulcerative colitis.

Study 827
The primary objective of this study was to assess the efficacy and safety of two dosing regimens of adalimumab for the induction of clinical remission in patients with moderately to severely active ulcerative colitis.

The secondary objective of this study was to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration.

Study Design
Study 826 (post Amendment 3)
This study was a Phase 3, multicenter, randomized, double-blind, and placebo-controlled study. The study was designed to evaluate the efficacy and safety of Humira for the induction of clinical remission in adult patients with UC.

Adult patients with UC were seen for a screening visit up to three weeks prior to randomization. Patients who met the inclusion criteria were randomized to receive treatment with Humira 160/80/40, Humira 80/40, or placebo (1:1:1).

The study was designed to include a 52-week treatment period. The double-blind treatment period lasted for eight weeks. Following the double-blind treatment period, patients had the option of enrolling in an open-label extension study during which patients continued to receive open-label Humira up to Week 52. During this open-label period, patients were given Humira or matched placebo every other week. If a patient

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met the definition of an inadequate responder (see Table 4 below), the investigator could increase the dose to Humira 40 mg weekly starting at Week 14.

Patients were seen for a study visit at screening, Weeks 0, 2, 4, 6, 8, 10, 12, 16, 22, 28, 36, 44, and 52/(end of study). Primary endpoint assessment occurred at Week 8. Patients could be seen for unscheduled study visits at any time during the study if they experienced worsening of UC symptoms. Patients also had a follow-up telephone visit to inquire about adverse events 70 days after the last dose of study drug.

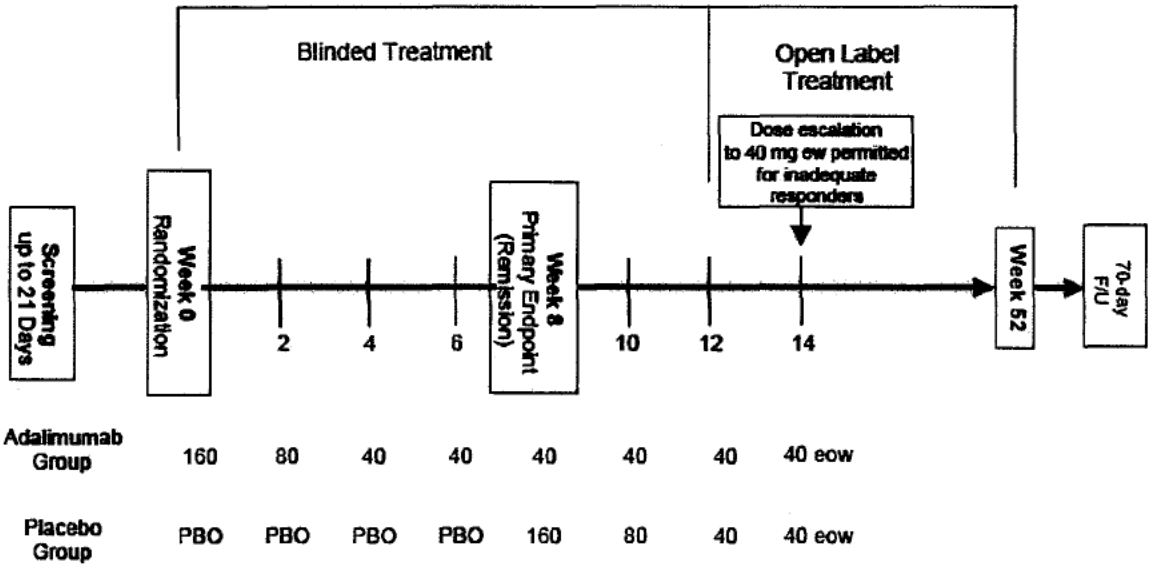
MO Comment:
Protocol Amendment 3 was introduced in August 2007 (approximately 8 months after the study started). Amendment 3 introduced significant changes in the design and implementation of Study 826. For additional information regarding protocol changes, see section 5.3.10. See

Figure 1 and
Figure **2** *below for a visual comparison of the design of Study 826 before and after the implementation of the changes of protocol Amendment 3. The most important design changes were as follows:*

1. *A new lower dose treatment arm (80/40 mg) was added. Initially, the study was planned to explore only a single dose of Humira (160/80/40 mg) versus placebo. The Applicant felt it was important to explore this lower dose of Humira given the early 2007 approval of both the 160/80/40 mg and 80/40 mg dosing regimens in the European Union for the induction of re**mission in adult patients with Crohn's** disease.*
2. *The earliest point in the study at which dose escalation was permitted changed from Week 14 to Week 12.*
3. *Induction dosing for patients initially randomized to placebo was eliminated. Instead, at Week 8 placebo patients began receiving a maintenance dose of 40 mg Humira every other week.*

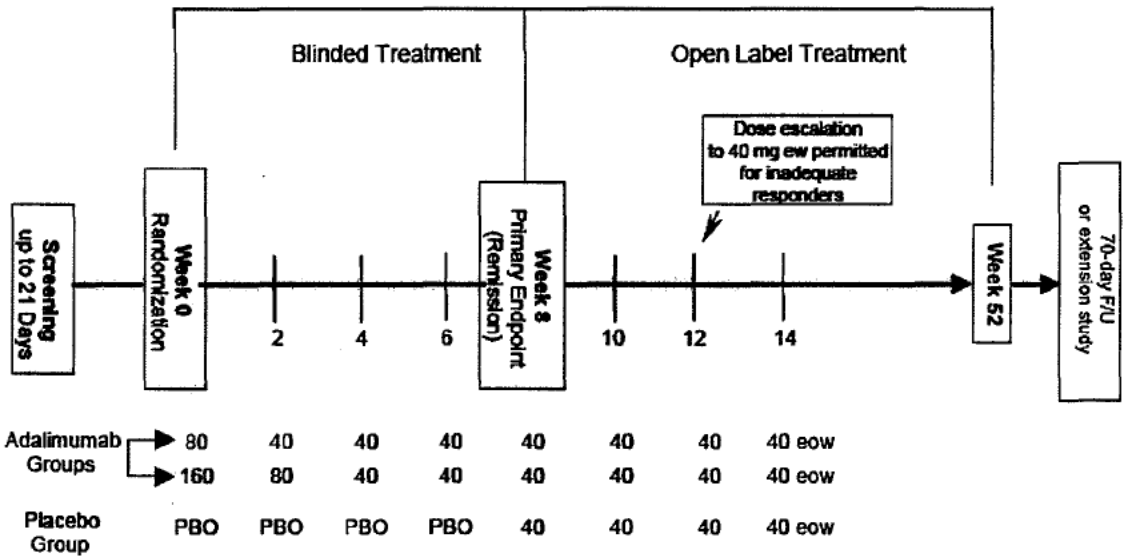
Because of these changes, the Applicant, in consultation with the FDA, designated that only patients enrolled after Amendment 3 would be included in the primary analysis set. Therefore, unless noted, in this review the design elements described for Study 826 refer to the study after protocol Amendment 3.

Figure 1. Design of Study 826 Prior to Amendment 3



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Figure 2. Design of Study 826 After Amendment 3



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Study 827

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial. The study was designed to evaluate the efficacy and safety of Humira for the induction and maintenance of remission in adult patients with moderately to severely active UC.

Adult patients with UC were seen for a screening visit up to three weeks prior to randomization. Patients who met the inclusion criteria were stratified by prior exposure to infliximab and/or other anti-TNF agents and randomized to receive treatment with Humira 160/80/40or placebo (1:1). Patients randomized to receive Humira were dosed with 160 mg at Week 0, 80 mg at Week 2, and 40 mg eow starting at Week 4. Placebo patients who met the criteria for inadequate response (see Table 4 below), could be switched to open-label Humira 40 mg eow beginning at Week 12.

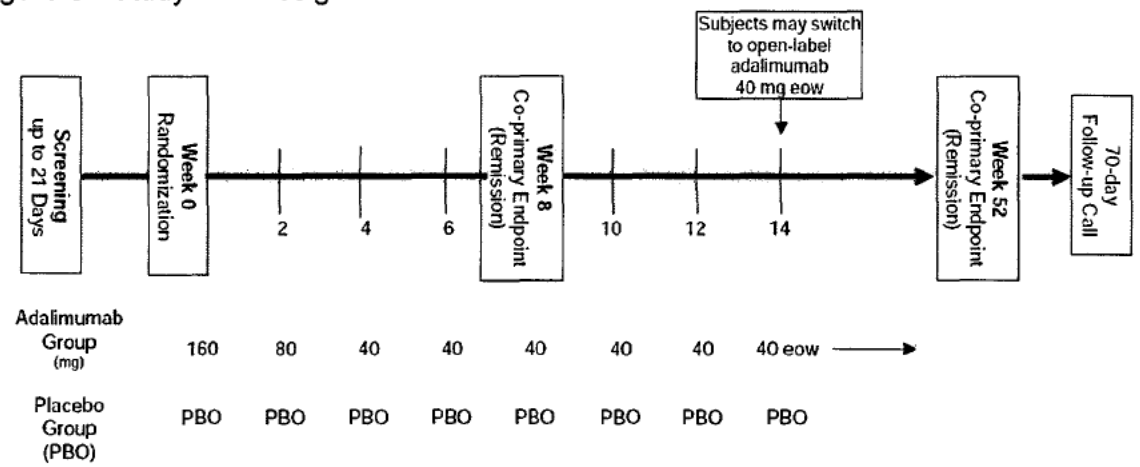
Any subject who demonstrated inadequate response at 2 consecutive visits at least 14 days apart while on open-label Humira was permitted to dose escalate to Humira 40 mg weekly.

Patients were seen for a study visit at screening, Weeks 0, 2, 4, 6, 8, 12, 16, 20, 26, 32, 38, 44, and 52/(end of study). The study had co-primary endpoints of induction of remission at Week 8 and maintenance of remission at Week 52. Patients could be seen for unscheduled study visits at any time during the study if they experienced worsening of UC symptoms. Patients also had a follow-up telephone visit to inquire about adverse events 70 days after the last dose of study drug.

Following the 52-week double-blind treatment period, patients had the option of continuing to receive Humira as part of an open-label extension study.

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Figure 3. Study 827 Design



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Table 4. Inadequate Responder Definition, Studies 826 and 827

Baseline partial Mayo score	Inadequate Responder Definition
4 to 7	Partial Mayo score greater than or equal to Baseline score on 2 consecutive visits at least 14 days apart
8 to 9	Partial Mayo score ≥ 7 on 2 consecutive visits at least 14 days apart

5.3.2 Key Inclusion Criteria

Studies 826 and 827

For inclusion, patients had to meet all of the following criteria at screening and at baseline:

1. Male or non-pregnant females ≥18 years of age.
2. Diagnosis of UC for greater than 90 days prior to Baseline.
3. Diagnosis of active UC confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy during the Screening Period, with exclusion of infection.
4. Active UC with a Mayo score of 6 to 12 points and endoscopy subscore of 2 to 3 points, despite concurrent treatment with at least 1 of the following (oral corticosteroids or immunosuppressants or both as defined below):
    a. Stable oral corticosteroid dose (prednisone dose of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline or stable oral corticosteroid dose (prednisone of < 20 mg/day) for at least 40 days prior to Baseline

and/or

b. At least a consecutive 90 day course of azathioprine or 6-mercaptopurine (6-MP) prior to Baseline, with a dose of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet formulation), or a dose that is the highest tolerated by the patient (e.g., due to leukopenia, elevated liver enzymes, nausea). Patient must be on a stable dose during that time. Subject was to be on a stable dose for at least 28 days prior to Baseline.

Note: If subjects were on both oral corticosteroid and immunosuppressants, only 1 of the drugs had to meet the above criteria. Concurrent therapy was not required for subjects who were previously treated with corticosteroids or immunosuppressants (azathioprine or 6-MP) during the previous 5 years and, in the judgment of the investigator, have failed to respond to or could not tolerate their treatment.

5. Females had to be either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or of childbearing potential and practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug. Examples of approved methods of birth control included the following:
   a. Condoms, sponge, foams, jellies, diaphragm or intrauterine device
   b. Oral, parenteral or intravaginal contraceptives for 90 days prior to study drug administration
   c. A vasectomized partner

   The results of the serum pregnancy test performed at the Screening Visit and urine pregnancy test performed at the Baseline Visit had to be negative.
6. Judged to be in generally good health by the investigator.

5.3.3 Key Exclusion Criteria

Patients were excluded, if they met any of the following criteria at screening or at baseline:

1. History of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Koch pouch, or ileostomy for ulcerative colitis or is planning bowel surgery.
2. Received infliximab or any other anti-TNF agent or any biological therapy in the past (Study 826). Received infliximab or any other anti-TNF agent and has not **clinically responded at anytime ("primary non-responder") unless patient** experienced a treatment limiting reaction (Study 827).
3. Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.
4. Received cyclosporine, tacrolimus, or mycophenolate mofetil within 60 days prior to Baseline.

5. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
6. Received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the Screening endoscopy and during the remainder of the Screening Period.
7. Current diagnosis of fulminant colitis and/or toxic megacolon.
8. Disease limited to the rectum (ulcerative proctitis).
9. Current diagnosis of indeterminate colitis or Crohn's Disease.
10. Currently receiving total parenteral nutrition.
11. Discontinued use of azathioprine or 6-MP within 28 days of Baseline.
12. Discontinued use of corticosteroid within 14 days of Baseline.
13. Using aminosalicylates for less than 90 days prior to Baseline, not on a stable dose for at least 28 days prior to Baseline, or discontinued use within 28 days of Baseline.
14. Current use of budesonide *and* prednisone (or equivalent).
15. Positive Clostridium difficile stool assay.
16. Presence of infection(s) requiring treatment with intravenous (IV) antibiotics, IV antivirals, or IV antifungals within 30 days prior to Baseline or oral antibiotics, oral antivirals, or oral antifungals within 14 days prior to Baseline.
17. History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix. Note: If the Screening colonoscopy/flexible sigmoidoscopy showed evidence of dysplasia or a malignancy, the subject was not to be enrolled in the study.
18. History of listeria, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus, immunodeficiency syndrome, central nervous system demyelinating disease, or untreated tuberculosis (TB).
19. Pregnancy or breast-feeding or considering becoming pregnant during the study. There should be at least a 150-day period between the last dose of study drug and either conception or initiation of breast-feeding in women of childbearing potential.
20. Poorly controlled medical condition(s), such as uncontrolled diabetes, unstable ischemic heart disease, moderate to severe congestive heart failure, recent cerebrovascular accident and any other condition, which in the opinion of the investigator, would put the subject at risk by participation in the protocol.
21. Received any investigational agent within 30 days or 5 half lives prior to Baseline (whichever was longer).
22. History of clinically significant drug or alcohol abuse during the previous year.
23. Known hypersensitivity to the excipients of adalimumab as stated in the label.
24. Prior exposure to Tysabri® (natalizumab).

5.3.4 Treatment

Once eligible for the study, patients were randomized to receive either Humira or placebo. Humira or matched placebo was supplied in 1 mL, pre-filled syringes containing 40 mg/0.8mL Humira or placebo for subcutaneous (SC) injection.

Study 826
Patients randomized to the highest dose group received 160 mg Humira at Week 0 and 80 mg Humira at Week 2. At Weeks 4 and 6, patients received 40 mg Humira or matched placebo.

Week 8 marked the end of the double-blind treatment portion of the study. At Week 8, patients randomized to the Humira treatment groups continued to receive 40 mg every other week until the end of the study (Week 52) and patients randomized to placebo began receiving Humira 40 mg every other week until Week 52/EOS. Dose escalation was allowed for inadequate responders after Week 12. See Table 4 for dose escalation criteria.

Table 5. Number of Study Drug Injections, Study 826 and Study 827

	Treatment Arm	Number of Humira 40 mg/0.8 mL injections	Number of 0.8mL placebo injections	Total number of injections/visit
Week 0	Humira 160/80/40	4	0	4
	Humira 80/40+	2	2	
	Placebo	0	4	
Week 2	Humira 160/80/40	2	0	2
	Humira 80/40+	1	1	
	Placebo	0	2	
Weeks 4 and 6	Humira 160/80/40	1	0	1
	Humira 80/40+	1	0	
	Placebo	0	1	
Week 8 to end of study (dose given every other week)*	Humira 160/80/40	1	0	1
	Humira 80/40+	1	0	
	Placebo	0	1	

* dose escalation to Humira 40 mg weekly was permitted if certain criteria were met, see section jkl for details
+ Study 827 did not include a Humira 80/40 treatment arm

Study 827
Patients randomized to treatment with Humira received 160 mg Humira at Week 0, 80 mg Humira at Week 2, and 40 mg Humira from Week 4 to end of study. Doses were administered subcutaneously every other week. Patients were allowed to dose escalate beginning at Week 12 if their response was deemed inadequate according to criteria described in Patients if their response to treatment was deemed inadequate. See Table 4 above for the definition of an "inadequate responder" and Table 5 for the number of injections per study visit.

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Patients randomized to placebo who met the criteria for inadequate response could have been switched to open-label Humira 40 mg eow beginning at Week 12. These patients were also allowed to dose escalate to Humira 40 mg weekly if they continued to meet criteria for inadequate response.

Studies 826 and 827

The dose, duration, and indication for all concomitant medications were to be recorded in each patient's file and CRF. All medications (including over-the-counter and herbals) were to be recorded. The CRF entry was to include all medications taken from 28 days prior to Week 0 including the dose, frequency, and reason(s) for use. Additionally, all medications for UC taken within 90 days of Week 0 were to be recorded. Patients who failed or were intolerant to corticosteroids or immunosuppressants within the previous 5 years were to record the highest previous dose administered.

Patients taking aminosalicylates, azathioprine, or 6-MP prior to Week 0 were to continue those medications at the pre-study doses. Patients taking probiotics were also to continue those medications at the pre-study dose. No adjustment of UC-related medications was allowed during the study with the exception of the following:

a) an oral corticosteroid taper between Week 8 and Week 52
b) a dose decrease of any UC-related concomitant treatments in the event of UC–treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator.

Prohibited concomitant medications were as follows:

- Live vaccines were (during the study and for 70 days after the last dose of study drug)
- Infliximab or any other anti-TNF agent
- Orencia® (abatacept) or any biological therapy
- Tysabri® (natalizumab)
- Kineret® (anakinra)
- Cyclosporine, tacrolimus, mycophenolate mofetil, and investigational agents (during the study and for 30 days or 5 half-lives prior to Week 0)
- Intravenous corticosteroids (during the study and within 14 days prior to Screening)
- Rectal therapy with any therapeutic enemas or suppositories (during the study and within 14 days prior to Screening and except those required for endoscopy

Study drug from Weeks 0 to 12 was administered during in-clinic visits by study site personnel, the patient, or the patient's designee. Injections during subsequent study visits were to be performed by the patient or designee under the supervision of trained medical personnel to reinforce proper aseptic SC injection technique. The patient was to maintain a dosing log with appropriate information recorded after each dosing and was to bring the log to each study visit. To document compliance, all syringes were to be

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counted and documented in the source document and on the appropriate drug accountability form.

5.3.5 Study Visits and Procedures

All study visits occurred in an outpatient setting. The study visits and related safety assessments are summarized in tables below.

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Table 6. Schedule of Study Assessments, Study 826

Procedures	Screening	Baseline Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 22	Week 28	Week 36	Week 44	Week 52/ Early Term[l]	70-Day Phone Follow-up Call[m]	Unscheduled Visit
Inclusion/Exclusion	X	X[a]														
Informed Consent	X															
Medical/Surgical Hx[b]	X	X														
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PPD[c]	X															
Chest X-ray[d]	X															
ECG[e]	X															
Pregnancy Test[f]	X	X												X		
C. difficile toxin	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Exam[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
General Lab[h]	X	X		X		X		X	X	X	X	X	X	X		
Urinalysis	X	X		X		X		X	X	X	X	X	X	X		
CRP		X		X		X		X	X					X		
Partial Mayo Score[i]		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Mayo Score		X				X								X		
Endoscopy	X[j]					X								X		
Biopsy for confirmation of UC	X															
IBDQ		X		X		X								X		
SF-36		X		X		X								X		

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Schedule of Study Procedures, Study 826 continued

Procedures	Screening	Baseline Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 16	Week 22	Week 28	Week 36	Week 44	Week 52/ Early Term[l]	70-Day Phone Follow-up Call[m]	Unscheduled Visit
Corticosteroid Taper[k]						X	X	X	X	X	X	X	X			
Resource Utilization Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing		X	X	X	X	X	X	X	X	X	X	X	X			X[n]

a. Inclusion/Exclusion Criteria at Baseline was an update since Screening.

b. Medical/surgical history at Baseline was an update since Screening.

c. Subjects with negative PPD test within 3 months of Screening were not required to repeat the skin test if documentation is available.

d. Subjects with normal chest x-ray (CXR) within 3 months of Screening were not required to repeat CXR if documentation was available.

e. Subjects with normal ECG within 3 months of Screening were not required to repeat ECGs if documentation is available.

f. Performed on all women - serum test at Screening, Week 52/Early Termination visit, urine test at Baseline.

g. Physical exams performed at Screening, Baseline, and Week 52/ET visits are full physical exams and those performed at all other visits were abbreviated and symptom-directed physical exams.

h. Blood draws were to be performed after completion of all clinical assessments and questionnaires.

i. Partial Mayo score includes stool frequency, rectal bleeding, and physician's global assessment.

j. Colonoscopy performed in subjects without a colonoscopy report available within 6 months of Screening. Flexible sigmoidoscopy performed in other subjects.

k. Subjects were permitted to undergo corticosteroid taper at or after Week 8.

l. Last dose of study drug was to be given either at Week 50 or 51, depending on whether subject was on a weekly or eow dosing schedule. Subjects were not to receive injection of study drug at Week 52 visit.

m. Site personnel were to contact all subjects approximately 70 days following study drug discontinuation to determine the occurrence of AEs.

n. Study drug could be dispensed at the Unscheduled Visit if there was a change in the dosing schedule or if damaged drug needed replacement.

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Table 7. Study 827 Study Assessments

Procedures	Scr	Baseline (Week 0)[a]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 26	Wk 32	Wk 38	Wk 44	Wk 52	ET	70-Day Phone FU Call[b]	Unscheduled Visit
Inclusion/Exclusion	X	X														
Informed Consent	X															
Medical/Surgical Hx	X	X														
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Purified Protein Derivative (PPD) Skin Test[c]	X															
Chest X-ray	X															
ECG	X															
Pregnancy Test[d]	X	X											X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
General Lab[f]	X	X		X	X	X		X	X	X	X	X	X	X		
Urinalysis[g]	X	X		X	X	X		X	X	X	X	X	X	X		
C. difficile toxin	X															
CRP	X	X		X	X	X				X			X	X		
ANA/dsDNA[h]		X								X			X	X		

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Table 5. Study 827 Study Assessments (cont'd)

Procedures	Scr	Baseline (Week 0)[a]	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 26	Wk 32	Wk 38	Wk 44	Wk 52	ET	70-Day Phone FU Call[b]	Unscheduled Visit
Inclusion/Exclusion	X	X														
Informed Consent	X															
Medical/Surgical Hx	X	X														
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Purified Protein Derivative (PPD) Skin Test[c]	X															
Chest X-ray	X															
ECG	X															
Pregnancy Test[d]	X	X											X	X		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
General Lab[f]	X	X		X	X	X		X	X	X	X	X	X	X		
Urinalysis[g]	X	X		X	X	X		X	X	X	X	X	X	X		
C. difficile toxin	X															
CRP	X	X		X	X	X				X			X	X		
ANA/dsDNA[h]		X								X			X	X		

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Table Study 827 Study Assessments (cont'd)

Scr – Screening; ET = Early Termination; FU = Follow-up

a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 3 day window is permitted around scheduled study visits. Medical/surgical history at Baseline is an update since Screening.
b. Site personnel will contact all subjects approximately 70 days following study drug discontinuation to determine the occurrence of AE's (see Section 6.4 for details).
c. PPD skin test is to be read 48-72 hours after placement.
d. Performed on all women - serum test at Screening and Week 52/Early Termination Visits; urine test at Baseline.
e. Physical examinations performed at Screening, Baseline, Week 8, Week 32, and Week 52/Early Termination Visits are full physical examinations and those performed at all other visits are abbreviated and symptom directed physical examinations.
f. Blood draws should be performed after completion of all clinical assessments and questionnaires.
g. Microscopic urinalysis performed if dipstick UA is abnormal, defined as where protein, blood, ketones or glucose is greater than trace.
h. Anti-dsDNA performed if ANA result is positive.
i. Partial Mayo Score, including stool frequency, rectal bleeding, and physician's global assessment.
j. Endoscopy results from Screening are used to calculate Mayo Score at Baseline Visit.
k. Subjects will complete the Work Productivity and Activity Impairment questionnaire on a weekly basis.
l. Subjects with satisfactory clinical response are permitted to begin corticosteroid taper at or after Week 8.
m. Collection of SAE's begins the day the Subject signs the informed consent.

5.3.6 Control Procedures

Randomization

Study 826 and Study 827
Randomization occurred centrally using an interactive voice response system (IVRS) at baseline. The randomization scheme used by the IVRS was generated by Abbott before the start of the study.

Placebo Control

Study 826 and Study 827
For both studies, Abbott manufactured a matched placebo for administration by subcutaneous injection. The matched placebo contained the inactive ingredients of the Humira formulation. See Table 8 below.

Table 8. Identity of Investigation Products, Studies 826 and 827

Study Drug	Formulation	Manufacturer	Bulk Lot Numbers
Adalimumab	40 mg/0.8 mL adalimumab/mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water for injections, sodium hydroxide added as necessary to adjust pH	Abbott	06-006764 07-011080 07-010526 07-014216 08-017131
Placebo for Adalimumab	mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water for injections, sodium hydroxide added as necessary to adjust pH	Abbott	06-006518 06-009051 06-006520 08-018846

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Blinding

Study 826 and Study 827
All study site personnel, investigators, and patients were to remain blinded to the treatment assignment. Abbott remained blinded until after the data from the double-blind phase was locked and the interim analysis was completed for Study 826. For Study 827,

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Data Management

Study 826 and Study 827
Pre-printed CRFs were used to collect information. All case report forms (CRFs) were to be compared to the source documentation. Once data was entered into the database, computer logic checks were run to check for inconsistencies. When inconsistencies were found, Data Clarification Forms (DCFs) were sent to the principal investigators for explanation.

For the analysis of clinical laboratory data the studies utilized regional central laboratories. For Study 826, sites in the US, Puerto Rico, and Canada shared central lab while sites in Europe shared use of a different central lab. For Study 827, one central lab was used for sites in the US, Canada, Australia, New Zealand, and Argentina while a separate central lab was used for sites in Europe and Israel.

5.3.7 Primary Efficacy Endpoint

Studies 826 and 827 used the same primary and secondary endpoint definitions. See **Table 9** for additional information. See Appendix A for a full description of the Mayo Score.

Study 826
The primary efficacy variable for this study was the proportion of patients in clinical remission at Week 8.

Study 827
The co-primary efficacy endpoint is the proportion of patients in clinical remission at Week 8 and the proportion of patients in clinical remission at Week 52.

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Table 9. Primary and Secondary Endpoint Definitions, Studies 826 and 827

Term	Definition
Remission	Mayo score ≤ 2 with no individual subscore > 1
Response per Mayo Score	A decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
Response per Partial Mayo Score	A decrease in Partial Mayo Score ≥ 2 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
IBDQ Responder	A subject with at least a 16 point increase from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score
Mucosal Healing	Endoscopy subscore of 0 or 1

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5.3.8 Secondary Efficacy Endpoint(s)

Study 826

Ranked secondary efficacy variables assessed at Week 8 included (in the statistical hierarchical order):

1. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 160/80/40 versus placebo).
2. Proportion of patients with mucosal healing at Week 8 (Humira 160/80/40 versus placebo).
3. Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
4. Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 160/80/40 versus placebo).
5. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira160/80/40 versus placebo).
6. Proportion of patients with clinical response per Mayo score at Week 8 (Humira 80/40 versus placebo).

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7. Proportion of patients with mucosal healing at Week 8 (Humira 80/40 versus placebo).
8. Proportion of patients with rectal bleeding sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
9. Proportion of patients with Physician's Global Assessment sub-score indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (Humira 80/40 versus placebo).
10. Proportion of patients with stool frequency sub-score indicative of mild disease (≤ 1) at Week 8 (Humira 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (Humira 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (Humira 80/40 versus placebo).

Non-ranked secondary efficacy variables:

- Proportion of patients with response per Partial Mayo Score at Weeks 2, 4, and 6.
- Proportion of patients with Rectal Bleeding sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Physician's Global Assessment sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of patients with Stool Frequency sub-score indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Change from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 8.
- Change from Baseline in SF-36 at Week 8.
- Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, and 8.
- Change from Baseline in Mayo Score at Week 8.
- Time to clinical response per Partial Mayo Score (up to Week 8).

Descriptive statistics were to be presented for the OL period of the study through Week 52, including, but not limited to, the following efficacy variables:

- Proportion of patients with remission at both Week 8 and at Week 52.
- Proportion of patients with remission at Week 52.
- Proportion of patients with response per Mayo Score at both Week 8 and Week 52.
- Time in clinical response per Partial Mayo Score.
- Proportion of patients with mucosal healing at both Week 8 and Week 52.
- Proportion of patients with mucosal healing at Week 52.
- Proportion of patients using corticosteroids at Baseline in remission at Week 8 who had discontinued corticosteroids and were in remission at Week 52.
- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids and were in remission at Week 52.

- Proportion of patients using corticosteroids at Baseline who had discontinued corticosteroids for at least 90 days and were in remission at Week 52.
- Time in steroid-free clinical response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients requiring dose escalation to 40 mg ew.
- Proportion of patients achieving response at Week 52 after dose escalation
- Proportion of patients achieving remission at Week 52 after dose escalation for a) patients who had not achieved response per Partial Mayo Score prior to dose escalation and b) patients who had achieved response per Partial Mayo Score but lost response (had inadequate response) prior to dose escalation.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding sub-score ≤ 1) at Week 52.
- Proportion of patients achieving minimal rectal bleeding (Rectal Bleeding sub-score ≤ 1) at both Week 8 and Week 52.
- Time in minimal rectal bleeding (Rectal Bleeding subscore ≤ 1).
- Proportion of patients randomized to placebo who achieve clinical response by Partial Mayo Score at Week 16.
- Proportion of patients who are IBDQ responders at Week 52.
- Change from Baseline in IBDQ at Week 52.
- Change from Baseline in SF-36 at Week 52.
- Change from Baseline in Mayo Score at Week 52.
- Change in Partial Mayo Score overtime.
- Colectomy rates during the study

Study 827

Ranked Secondary Variables:

1. Proportion of patients with remission (sustained) at both Weeks 8 and 52.
2. Proportion of patients who achieve response per Mayo Score at Week 8 and Week 52.
3. Proportion of patients who discontinue corticosteroid use and achieve remission at Week 52.
4. Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 52.
5. Proportion of patients with response per Mayo Score (sustained) at both Weeks 8and 52.
6. Proportion of patients who discontinue corticosteroid use and achieve remission (sustained) at both Weeks 32 and 52.
7. Proportion of patients who are IBDQ responders at Week 52.
8. Proportion of patients who are IBDQ responders at Week 8.

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Non-ranked Secondary Variables:

- Proportion of patients who achieve clinical remission at Week 32.
- Proportion of patients who achieve remission (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve clinical response at Week 32.
- Proportion of patients who achieve response per Mayo Score (sustained) throughout Weeks 8, 32, and 52.
- Proportion of patients who achieve response per Partial Mayo Score over time.
- Time to response per Partial Mayo Score.
- Time in response per Partial Mayo Score.
- Proportion of patients who discontinue corticosteroid use for at least 90 days and achieve remission at Week 32.
- Proportion of patients who discontinue corticosteroid use and achieve remission at Week 32.
- Proportion of patients who have discontinued corticosteroid use at each time point after Week 8.
- Time in steroid-free response per Partial Mayo Score for patients who were using corticosteroids at Baseline.
- Proportion of patients who are IBDQ responders at Week 32.
- Proportion of patients who are IBDQ responders (sustained) at both Weeks 8 and 52.
- Proportion of patients who are IBDQ responders (sustained) throughout Weeks 8, 32 and 52.
- Proportion of patients with IBDQ score ≥ 170 over time.
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score over time.
- Change from Baseline in Short Form-36 Questionnaire (SF-36) over time.
- Change from Baseline in Mayo Score over time.
- Change from Baseline in endoscopy score over time.

5.3.9 Statistical Information

Study 826

The primary analysis was conducted in the ITT-A3 population (see Table 10 below). A non-responder imputation (NRI) method was used to calculate the remission rate. Patients who discontinued the study for any reason prior to Week 8 and patients with a missing Mayo score at Week 8 were counted non-remitters. As a sensitivity analysis, the remission rate was also calculated using a last observation carried forward (LOCF) method.

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The normal approximation to the binomial distribution was used to construct the two-sided 95% confidence interval (CI) for the difference in the remission rate between each Humira treatment group and the placebo group. The above analyses were also carried out in the ITT-A2 Population and the Per Protocol Population to provide supportive evidence of efficacy.

The sample size was calculated using the assumption that 15% of subjects in the placebo group would achieve clinical remission at Week 8. Using this assumption, a sample size of 125 per treatment group in the ITT-A3 population would be adequate to detect a 15% difference using a chi-square test with 80% power at a 0.05 two-sided significance level.

Table 10. Population Definitions, Study 826

Population	Definition
Intent-To-Treat – E	All patients with confirmed UC at Baseline who were randomized at any time during the study and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo
ITT-A3	All patients with confirmed UC at Baseline who were randomized according to the revised study design described in Amendment 3 (and Amendment 4) and received at least 1 injection of the following induction regimens: Humira 160/80/40 mg, Humira 80/40 mg, or placebo
Safety	All patients who received at least 1 injection of study drug.
Per Protocol	All ITT-A3 patients without major protocol deviations

Because two doses of Humira were used in Study 826, the following hierarchical order was used to handle the multiplicity issues induced by the two comparisons to placebo:

1. Compare the remission rates of Humira 160/80/40 mg group and placebo at Week 8. The superiority of Humira 160/80/40 mg treatment over placebo was to be established by the Chi square test (two-sided) at an alpha level of 0.05.
2. Compare the remission rates of Humira 80/40 mg group and placebo at Week 8. The superiority of Humira 80/40 mg treatment over placebo was to be established by the Chi square test (two-sided) at an alpha level of 0.05.

A p-value $\leq$ 0.05 from Comparison 1 was necessary to initiate Comparison 2 at a significance level of 0.05. Since a hierarchical procedure was used, each comparison was to be tested at a significance level of 0.05 and overall alpha level of 0.05 could be preserved.

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The safety analyses were conducted in the safety population.

Study 827

Efficacy analyses were to be conducted on the intent-to-treat (ITT) analysis set. This population was defined as all randomized patients who received at least one dose of study drug. The primary efficacy analysis used the NRI approach to impute missing values. For other efficacy analyses, the observed cases (OC) and LOCF methods were used, as appropriate.

The LOCF approach was used as a sensitivity analysis of the primary and secondary endpoint analyses. The following rules were used for the LOCF approach:

1. Baseline and pre-Baseline values were not to be used to impute the missing post-Baseline values.
2. Missing values after study Day 1 were imputed using the latest non-missing values after Day 1 and prior to the missing value.
3. For subjects who switched to OL administration, the latest non-missing value before or at the visit when the subject switched to OL administration was to be carried forward.

Observed case (OC) analyses were only performed as sensitivity analyses. For the primary analysis, OC was performed on data only until the switch to open-label administration. For the analysis of colectomy rates, OC analysis was performed on data during the DB, OL, and follow-up periods. For specific dose-escalation analyses, OC analyses were performed on data after dose-escalation to Humira 40 mg ew. Missing values were not used in an OC analysis.

The safety analyses were conducted in the safety population.

5.3.10 Protocol Amendments

Study 826

The original protocol was amended 4 times. The most significant changes to the protocol occurred with Amendment 3 which was finalized after the study began.

Amendment 1 was finalized 10 August 2006 (before the study began). The change was introduced for the following primary reasons:

1. **To clarify the definition of "response" per partial Mayo score.**
2. To clarify the management of patients who developed dysplasia or malignancy of the gastrointestinal tract during the study.
3. To clarify that continued participation of a patient diagnosed with a carcinoma *in situ* is at the discretion of the investigator.

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Amendment 2 was finalized 27 October 2006 (before the study began). The change was introduced for the following primary reasons:

1. To revise inclusion criterion No. 4 to permit patients requiring maintenance doses of 10 mg/day to 20 mg/day prednisone or equivalent for at least 40 days.
2. To provide direction on the management of patients who exhibit persistent inadequate response while on Humira weekly.
3. To expand the list of prohibited medications to include concurrent biological therapy, Tysabri, and other investigational agents.

Amendment 3 was finalized 06 August 2007 (approximately 8 months after the study began). The change was introduced for the following primary reasons:

1. To change the blinded study drug period from 12 weeks to 8 weeks and add the 80/40 mg Humira induction dosing arm.
2. To revise the inclusion criteria to clarify that current therapy with either a corticosteroid or an immunosuppressant will satisfy these inclusion criteria and to simplify the interpretation of the corticosteroid dosage requirements.
3. To expand the birth control methods listed in the inclusion criteria.
4. To expand the exclusion criteria to include any prior biological therapy and not just infliximab or other anti-TNF agents.
5. To remove methotrexate as an exclusionary medication.
6. To decrease the exclusionary duration for therapy with cyclosporine, tacrolimus, or mycophenolate mofetil from 60 days to 30 days prior to Baseline.
7. To expand prohibited therapies to exclude biologic therapies including natalizumab and abatacept.
8. To add colectomy rates as a secondary efficacy variable.
9. To revise the sample size determination to reflect the inclusion of an additional adalimumab treatment arm.

Amendment 4 was finalized 12 March 2009 (approximately 2 years, 4 months after the study began). The change was introduced to update the contact information for various study personnel and to update the statistical section of the protocol to reflect changes in the secondary efficacy variables.

Study 827

The original protocol was amended globally twice and underwent 5 administrative changes.

Amendment 1 was finalized 13 September 2007 (after the study began). The change was introduced for the following primary reasons:

1. To revise inclusion criterion No. 4 to clarify that current therapy with either a corticosteroid or an immunosuppressant will satisfy this criterion.
2. To expand the choices of acceptable birth control and clarify that patients should remain on birth control for at least 150 days after the last dose of study drug.

3. To remove methotrexate as an exclusionary medication and change the exclusionary duration for therapy with cyclosporine, tacrolimus, or mycophenolate mofetil from 60 days to 30 days prior to Week 0.
4. To exclude patients with severe congestive heart failure in order to conform to current Humira labeling.
5. To expand the list of prohibited therapies to include Tysabri® (natalizumab) and Orencia® (abatacept).
6. To remove the requirement for CXR and/or ECG at baseline for patients with a normal CXR and/or ECG within 3 months of screening.
7. To add colectomy rate as a secondary endpoint.

Amendment 2 was finalized 15 October 2007 (after the study began). The change was introduced for the following primary reasons:

1. To revise the primary and secondary efficacy variables to align with EMEA guidance documents. Strict ordering of ranked co-primary and secondary variables was implemented.
2. To revise the analysis method for discrete demographic variables to the Chi-square test.

6 Review of Efficacy

Efficacy Summary

For a full discussion of the efficacy summary results, see the Risk Benefit Assessment in Section 1.2 above.

6.1 Indication

The Applicant is proposing that Humira receive an indication for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

6.1.1 Methods

Section 5.3 contains a discussion of the study protocols; Section 6 contains the study results.

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6.1.2 Demographics

Baseline demographic characteristics for the ITT-A3 population of Study 826 and the ITT population of Study 827 are presented in Table 11 below. These populations represent the primary efficacy analysis populations of each of these studies. Both studies randomized a predominance of white male patients in the range of 40 to 65 years of age. In both studies, randomization produced demographic subgroups which were well-balanced between treatment groups.

Table 11. Demographics, Studies 826 and 827

Demographic Subgroup	Study 826 (ITT-A3 Population)			Study 827 (ITT Population)	
	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Placebo	Humira 160/80/40 mg
N	130	130	130	246	248
Sex (n,%)					
Male	82 (63.1)	78 (60.0)	83 (63.8)	152 (61.8)	142 (57.3)
Female	48 (36.9)	52 (40.0)	47 (36.2)	94 (38.2)	106 (42.7)
Age range (years) (n,%)					
< 40 years	72 (55.4)	63 (48.5)	74 (56.9)	118 (48.0)	136 (54.8)
40 to ≤ 64 years	54 (41.5)	59 (45.4)	51 (39.2)	116 (47.2)	105 (42.3)
≥ 65 years	4 (3.1)	8 (6.2)	5 (3.8)	12 (4.9)	7 (2.8)
Mean ± SD	38.9 ± 12.68	41.6 ± 13.99	38.2 ± 13.46	41.3 ± 13.22	38.6 ± 12.47
Race (n,%)					
Caucasian	117 (90.0)	119 (91.5)	119 (91.5)	234 (95.1)	236 (95.2)
Black	5 (3.8)	6 (4.6)	2 (1.5)	4 (1.6)	7 (2.8)
Hispanic	5 (3.8)	6 (4.6)	4 (3.1)	7 (2.8)	6 (2.4)
Asian	5 (3.8)	5 (3.8)	7 (5.4)	4 (1.6)	1 (0.4)
Other	3 (2.3)	0	2 (1.5)	4 (1.6)	4 (1.6)
Weight					
(mean ± SD), kg	78.7 ±17.42	76.8 ± 15.01	75.5 ± 14.20	77.1 ± 17.31	75.3 ± 17.71
Nicotine use (n,%)					
User	7 (5.4)	8 (6.2)	12 (9.2)	19 (7.8)	20 (8.1)
Ex-user	35 (26.9)	46 (35.4)	37 (28.5)	88 (35.9)	94 (37.9)
Never used	88 (67.7)	76 (58.5)	81 (62.3)	138 (56.3)	134 (54.0)
Alcohol use (n, %)					
Drinker	57 (43.8)	62 (47.7)	62 (47.7)	125 (51.0)	132 (53.2)
Ex-drinker	7 (5.4)	5 (3.8)	9 (6.9)	11 (4.5)	8 (3.2)
Non-drinker	66 (50,8)	63 (48.5)	59 (45.4)	109 (44.5)	108 (43.5)

Study 826 CSR, Table 11 p 191 and Study 827 CSR Table 8 p 226

6.1.3 Subject Disposition

Study 826

In Study 826, there were a total of 576 patients randomized. These patients were randomized to placebo (223), Humira 80/40 mg (130), and Humira 160/80/40 mg (223). A total of 575 patients were included in the ITT-E set and 390 patients were randomized

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after Protocol Amendment 3 and were included in the ITT-A3 set (the pre-specified primary analysis set).

While 118 patients (30.3%) discontinued Study 826 prior to completion, only 30 patients (7.7%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (5.4%) and lack of efficacy (3.3%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira dosage groups prior to Week 8 and during the entire Study. See Table 12 for additional patient disposition information.
MO Comment:
For efficacy considerations, only those patients who discontinued prior to Week 8 are noteworthy given that Study 826 was designed as an induction study (primary endpoint, remission rate at Week 8).

Study 827
There were a total of 518 patients randomized into Study 827 at 103 global sites. Of those patients randomized, 24 patients from 3 sites were excluded form the ITT analysis set due to site non-compliance.

These patients were randomized to placebo (223), Humira 80/40 mg (130), and Humira 160/80/40 mg (223). A total of 575 patients were included in the ITT-E set and 390 patients were randomized after Protocol Amendment 3 and were included in the ITT-A3 set (the pre-specified primary analysis set).

While 118 patients (30.3%) discontinued Study 826 prior to completion, only 30 patients (7.7%) discontinued prior to the completion of Week 8. Of those patients who discontinued prior to Week 8, the primary reasons for discontinuation were adverse events (5.4%) and lack of efficacy (3.3%). The number of premature discontinuations for lack of efficacy was similar across the placebo and Humira dosage groups prior to Week 8 and during the entire Study. See Table 12 for additional patient disposition information.

Table 12. Patient Disposition, Study 826, ITT-3 population

	Study 826, ITT-A3 Population				Study 827, ITT Population		
	Placebo	Humira 80/40	Humira 160/80/40	TOTAL	Placebo	Humira 160/80/40	TOTAL
Randomized	130	130	130	390	246	248	518
Completed Study	91 (70.0)	86 (66.2)	95 (73.1)	272 (69.7)	131 (53.3)	164 (66.1)	309 (59.7)
Discontinued Early[a]	39 (30.0)	44 (33.8)	35 (26.9)	118 (30.3)	115 (46.7)	94 (37.9)	209 (42.3)
Lack of efficacy	26 (20.0)	22 (16.9)	17 (13.1)	65 (16.7)	70 (28.5)	63 (25.4)	133 (26.9)
AE/SAE	22 (16.9)	19 (14.6)	14 (10.8)	55 (14.1)	25 (10.2)	12 (4.8)	37 (7.5)
Withdrew consent	3 (2.3)	9 (6.9)	5 (3.8)	17 (4.4)	4 (1.6)	8 (3.2)	12 (2.4)
Protocol violation	1 (0.8)	1 (0.8)	3 (2.3)	5 (1.3)	5 (2.0)	1 (0.4)	6 (1.2)
Lost to follow-up	0	3 (2.3)	1 (0.8)	4 (1.0)	0	1 (0.4)	1 (0.2)
Other[b]	0	4 (3.1)	1 (0.8)	5 (1.3)	11 (4.5)	9 (3.6)	20 (4.0)
Discontinued prior to Week 8	9 (6.9)	12 (9.2)	9 (6.9)	30 (7.7)	36 (14.6)	23 (9.3)	59 (11.9)
AE/SAE	6 (4.6)	7 (5.4)	4 (3.1)	17 (4.4)	10 (4.1)	5 (2.0)	15 (3.0)
Withdrew consent	0	4 (3.1)	1 (0.8)	5 (1.3)	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0	2 (1.5)	0	2 (0.5)	0	0	0
Lack of efficacy	5 (3.8)	5 (3.8)	2 (1.5)	12 (3.1)	15 (6.1)	13 (5.2)	28 (5
Protocol violation	0	0	2 (1.5)	2 (0.5)	3 (1.2)	1 (0.4)	4 ((
Other[c]	0	0	1 (0.8)	1 (0.3)	6 (2.4)	3 (1.2)	9 (1.8)

Study 826, CSR pp. 181-182/3375 AND Study 827 CSR. Study 827, CSR p. 220, Table 5

a. Primary reason, patients could have discontinued for more than one reason

b. **Reasons recorded as "other" included:** diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator discretion, non-compliance, positive TB skin test, patient wanted to start a family, and total colectomy within the 70-day follow-up period

c. patient diagnosed with CD

A number of patients in the ITT-A3 population had major protocol violations, as defined by ICH guidelines. Major protocol violations that had the potential to impact the primary efficacy analysis were accounted for by excluding those patients from the Per Protocol Set.

Table 13. Major Protocol Violations, ITT-E and ITT-A3 Populations

	Placebo	Humira 80/40 mg	Humira 160/80/40 mg	Total
Total ITT-E patients	222	130	223	575
Failed inclusion /exclusion criteria	24 (10.8%)	9 (6.9%)	11 (4.9%)	44 (7.7%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.3%)	1 (0.2%)
Wrong treatment or incorrect dose	12 (5.4%)	10 (7.7%)	14 (6.3%)	36 (6.3%)
Prohibited Concomitant medication	19 (8.6%)	13 (10.0%)	14 (6.3%)	46 (8.0%)
Total ITT-A3 patients	130	130	130	390
Failed inclusion /exclusion criteria	8 (6.2%)	9 (6.9%)	8 (6.2%)	25 (6.4%)
Developed withdrawal criteria/was not withdrawn	0	0	1 (0.8%)	1 (0.3%)
Wrong treatment or incorrect dose	10 (7.7%)	10 (7.7%)	11 (8.5%)	31 (7.9%)
Prohibited Concomitant medication	11 (8.5%)	13 (10.0%)	8 (6.2%)	32 (8.2%)

Study 826 CSR Tables 14.1_2.3 and 2.4 pp 517-518/3375

6.1.4 Analysis of Primary Endpoint(s)

INDUCTION OF REMISSION

Study 826

The primary endpoint for induction of remission was the proportion of patients in remission per Mayo Score. To meet remission criteria, patients had to have a Mayo score of ≤ 2 with no individual sub-score > 1. The statistical analysis plan (SAP) pre-specified that the primary analysis population for Study 826 was the intent-to-treat population enrolled after Protocol Amendment 3 (ITT-A3).

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The difference in the rates of remission at Week 8 was not statistically significant between patients taking placebo and patients taking Humira 80/40 mg.

For patients taking Humira 160/80/40, the treatment difference was 9.3% (Humira-placebo) and the p-value was 0.031 using the Chi-squared exact test of significance. This was the pre-specified primary analysis set. See Table 14 below.

Table 14. Induction of Remission Rate (Week 8), Study 826 Results

Study	Analysis Set	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value	Test of Significance
826	ITT-A3	9.2% (12/130)	18.5% (24/130)	9.3%	0.031	Chi-squared
Same as above					**0.047**	**Fisher's** Exact Test

Non-responder imputation (NRI) - all patients with missing remission values were considered to be non-remitters

MO Comment:
***If Fisher's exact test is used to calcul**ate the p-value for Study 826 (induction of remission), the statistical significance of the difference between placebo and Humira 160/80/40 dose groups is borderline, p=0.0471. Interpreting the statistical significance of the results of Study 826 is dependent upon which test of significance is used. It appears that the data of Study 826 are not robust given that the conclusion reached about the statistical significance of the study results depends on which test of significance [of two appropriate tests] is used.*

To further evaluate the robustness of the Study 826, Dr. Fan conducted a sensitivity analysis to determine how a 0.8% change in remission status would affect the p-value **(Fisher's Exact Test). The 0.8% change** was equivalent to one patient. For this analysis, sample sizes were fixed and 2 cases were considered. In case 1, the Humira 160/80/40 remission rate was changed by -0.8% from 18.5% to 17.7% and the placebo remission rate remained unchanged at 9.2%. In case 2, the Humira remission rate was not changed (18.5%) and the placebo remission rate was changed by +0.8% to 10.0%. The sensitivity analysis revealed that a change in the remission status of one patient in the Humira group (from remitter to non-remitter) or one patient in the placebo group (from non-remitter to remitter) would change the p-value (F**isher's exact test) from** borderline significance to non-significant. See Table 15 below.

Table 15. Remission Rate, 0.8% Change Sensitivity Analysis

	Placebo	Humira 160/80/40 mg	Difference	p*-value
Original ITT-A3 Data	9.2%	18.5%	9.3%	0.0471
Case 1	17.7%	9.2%	8.5%	0.0681
Case 2	10.0%	18.5%	8.5%	0.0748

Non-responder imputation (NRI) - all patients with missing remission values were considered to be non-remitters
*p-value calculated using **Fisher's Exact Test**

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Sensitivity Analyses

The Applicant conducted sensitivity analyses using different patient populations and missing data imputation methods. See Table 16 below.

Table 16. Sensitivity Analyses (ITT-A3, PP, and IT-Esets), Study 826

	Placebo	Humira 80/40 mg	p-value	Humira 160/80/40 mg	p-value
ITT-A3 (LOCF)[a]	9.8% (12/123)	10.8% (13/120)	0.782	19.4% (24/124)	0.033
PP (NRI)	8.3% (10/120)	9.8% (12/122)	0.684	18.5% (23/124)	0.020
ITT-E (NRI)	7.2% (16/222)	10.0% (13/130)	0.358	15.7% (35/223)	0.005

Adapted from Applicant's Table 35, Study 826 CSR p 224/3375
LOCF = last observation carried forward; NRI = non-responder imputation
a. p values for adalimumab versus placebo in ITT-A3 set (NRI and LOCF analyses) and placebo set from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5). For subjects in the ITT-E set, the P value to compare adalimumab 160/80/40 versus placebo is from CMH test with subjects in/not in the ITT-A3 set as the stratification factor; and the p value to compare adalimumab 80/40 versus placebo is from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5).
b. Per the LOCF analysis, the last non-missing post-Baseline values were carried forward.

MO Comment:
In the sensitivity analyses presented in Table 16, the treatment differences continue to remain small.

To determine if there was a difference in efficacy based on Mayo score at baseline, Dr. Fan (statistical reviewer) performed a *post-hoc* analysis of remission by baseline Mayo score. These results show that the highest remission rate was seen in patients with the lowest baseline Mayo score (33.3%, baseline Mayo score=6). Patients with the lowest baseline Mayo score also had the highest placebo remission rate resulting in a **treatment difference (Humira–p**lacebo) of only 10.1%. The largest treatment difference was seen in patients with baseline Mayo scores of 11 and 12. For both these groups, the placebo remission rate was 0%. There were very few patients in each Mayo score subgroup and the study was not powered to detect this level of difference. However, when results are combined and an overall p-value is obtained for the difference in remission rate at Week 8 controlling for Mayo score at baseline, the p-value is not significant, 0.0852.

Table 17. Remission at Week 8 by Baseline Mayo Score, Study 826

Mayo Score at baseline	Placebo Rate	Humira160/80/40 Rate	p-value[a]
6	2/9 (22.2%)	5/15 (33.3%)	
7	1/28 (3.6%)	2/13 (15.4%)	
8	4/19 (21.1%)	5/24 (20.8%)	
9	3/27 (11.1%)	5/33 (15.2%)	
10	2/34 (5.9%)	3/25 (12.0%)	
11	0/8 (0.0%)	3/15 (20.0%)	
12	0/5 (0.0%)	1/5 (20.0%)	
Combined			**0.0852**

Adapted from Table by M. Fan, PhD, statistical reviewer.
[a] p-values obtained from Cochran-Mantel-Haenszel test.

In a 23 November 2010 pre-sBLA Meeting with the Applicant, the Division recommended a *post hoc* analysis of the remission endpoint using a different definition of remission. Specifically, the Agency recommended that remission be defined as:

a. Total Mayo score ≤2
b. Rectal bleeding subscore=0 (no bleeding)
c. Endoscopy subscore=0 (e.g., no friablility).

This analysis was recommended because this new definition of clinical remission is more in line with current Division thinking regarding the necessary components for clinical remission. The Applicant completed this analysis and included the results in the Integrated Summary of Efficacy (ISE).

During FDA review of the submission, it was discovered that the revised definition of remission given to the Applicant during the pre-sBLA meeting had not explicitly stated the criterion that no individual subscore could be >1; this was the intended revised definition of remission. Dr. Milton Fan, statistical reviewer, performed a *post-hoc* sensitivity analysis using the intended revised FDA remission definition that included all of the following:

a. Total Mayo score ≤2
b. Rectal bleeding subscore=0 (no bleeding)
c. Endoscopy subscore=0 (e.g., no friablility)
d. No individual subscore >1.

The difference between the two analyses (ITT-A3 analysis set, Study 826) was two patients in the Humira 160/80/40 treatment group. Both patients had a total Mayo score

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of 2. However, both patients also had stool frequency subscores of 2. Therefore, according to the remission definition given to the Applicant, these patients were counted as being in remission. However, according to the *intended* FDA definition (i.e., includes the criterion that no individual subscore could be >1), these patients should have been counted as not being in remission. See Table 18 below for results of remission rate analysis using the *intended* FDA definition of remission.

Table 18. Remission Rate (Week 8), Intended FDA Remission Definition*

ITT-A3	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value
Remission Rate	4.6% (6/130)	11.5% (15/130)	6.9%	0.067

* Intended FDA Remission Definition: Total Mayo score ≤2, Rectal bleeding subscore=0 (no bleeding), Endoscopy subscore=0 (e.g., no friablility), and No individual subscore >1.
p-values calculated using **Fisher's Exact test.**
Modified from Table in Statistical Review by M. Fan, PhD
NRI Method used for missing data imputation

MO Comment:
Currently, the Division regards absence of rectal bleeding and lack of friability on endoscopy as necessary components of remission. When the intended FDA definition of remission (i.e., includes the criterion that no individual subscore could be >1) was used, the difference between the rate of remission for the placebo and Humira groups was not statistically significant. When the FDA definition (as interpreted by the Applicant) was used (see discussion above), the p-value for the difference between treatment groups was statistically significant (p=0.027). This further illustrates how a change in the remission status of one or two patients can alter the statistical significance of the study results. This reviewer believes that the induction data from Study 826 are not robust and do not provide convincing evidence that Humira 160/80/40 is more efficacious than placebo.

Subgroup Analysis
Subgroup analysis of the primary induction endpoint revealed that the 95% confidence interval for the difference between Humira and placebo included zero for most subgroups (p-value >0.05). Exceptions included white race, CRP <10.0 mg/L, current smoker, and use of azathioprine and 6-mercaptopurine at baseline. See Table 19 below.

Table 19. Subgroup Analysis of Primary Induction Endpoint, Study 826

Subgroup	Placebo Rate	Adalimumab 80/40 Rate	95% CI	Adalimumab 160/80/40 Rate	95% CI
Gender					
Male	7/82 (8.5%)	7/78 (9.0%)	(-8.3%, 9.2%)	13/83 (15.7%)	(-2.8%, 17.0%)
Female	5/48 (10.4%)	6/52 (11.5%)	(-11.1%, 13.4%)	11/47 (23.4%)	(-1.9%, 27.9%)
Age					
<40	9/72 (12.5%)	8/63 (12.7%)	(-11.0%, 11.4%)	16/74 (21.6%)	(-3.0%, 21.2%)
40-64	3/54 (5.6%)	4/59 (6.8%)	(-7.6%, 10.1%)	7/51 (13.7%)	(-3.1%, 19.4%)
≥65	0/4 (0.0%)	1/8 (12.5%)	(-10.4%, 35.4%)	1/5 (20.0%)	(-15.1%, 55.1%)
Race					
White	10/117 (8.5%)	12/119 (10.1%)	(-5.9%, 8.9%)	22/119 (18.5%)	(1.3%, 18.6%)
Non-white	2/13 (15.4%)	1/11 (9.1%)	(-32.2%, 19.7%)	2/11 (18.2%)	(-27.3%, 32.9%)
Weight					
< 70 kg	5/35 (14.3%)	6/40 (15.0%)	(-15.3%, 16.7%)	11/45 (24.4%)	(-6.9%, 27.2%)
≥70 kg	7/95 (7.4%)	7/90 (7.8%)	(-7.2%, 8.0%)	13/85 (15.3%)	(-1.4%, 17.2%)
CRP					
<10.0 mg/L	7/95 (7.4%)	9/87 (10.3%)	(-5.3%, 11.3%)	21/101 (20.8%)	(3.9%, 22.9%)
≥10.0 mg/L	4/32 (12.5%)	4/40 (10.0%)	(-17.3%, 12.3%)	2/25 (8.0%)	(-20.1%, 11.1%)
Smoker					
Ex-smoker	2/35 (5.7%)	4/46 (8.7%)	(-8.2%, 14.2%)	6/37 (16.2%)	(-3.6%, 24.7%)
Smoker	0/7 (0.0%)	1/8 (12.5%)	(-10.4%, 35.4%)	4/12 (33.3%)	(6.7%, 60.0%)
Non-smoker	10/88 (11.4%)	8/76 (10.5%)	(-10.4%, 8.7%)	14/81 (17.3%)	(-4.7%, 16.5%)
Corticosteroid Use at baseline					
Yes	8/89 (9.0%)	9/74 (12.2%)	(-6.4%, 12.7%)	12/71 (16.9%)	(-2.6%, 18.5%)
No	4/41 (9.8%)	4/56 (7.1%)	(-13.9%, 8.7%)	12/59 (20.3%)	(-3.1%, 24.3%)
Azathioprine and 6-Mercapto-purine therapy at baseline					
Yes	2/52 (3.8%)	6/51 (11.8%)	(-2.4%, 18.2%)	8/51 (15.7%)	(0.6%, 23.1%)
No	10/78 (12.8%)	7/78 (8.9%)	(-13.7%, 5.8%)	16/79 (20.3%)	(-4.1%, 19.0%)

Reproduced from Statistical Review by Milton Fan, PhD
95% CI based on normal approximation to the binomial distribution.

MO Comment:
The lack of statistically significant primary efficacy results in most subgroups brings into further question whether a difference in remission rate actually exists between the Humira and placebo treatment groups. It is expected that a statistically significant difference (if one exists) would be seen in the subgroups with large numbers of patients including males, females, ages <40, weight ≥75 kg, and corticosteroid use at baseline.

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Study 827

In Study 827, ranked co-primary endpoint evaluation was carried out in a hierarchical fashion using a two-sided Cochran-Mantel-Haenszel (CMH test) adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 8 was tested first. The primary analysis set for Study 827 was the ITT population (all patients who received at least one dose of study drug during the double-blind treatment period).

Analysis of the primary endpoint revealed that at Week 8 the remission rate in patients taking Humira (16.5%) was statistically significantly higher than in patients taking placebo (7.2%), p-value=0.019.

Table 20. Primary Induction Endpoint, Study 827

Study	Analysis Set	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p*-value
827	ITT	9.3% (23/246)	16.5% (41/248)	7.2%	0.019

*p-value calculated using CMH test adjusted for prior anti-TNF exposure

MO Comment:
Similar to Study 826, the treatment difference in Study 827 was small (7.2%).

Sensitivity Analyses

The Applicant conducted sensitivity analyses using different patient populations and missing data imputation methods.

Table 21. Sensitivity Analyses (mITT, PP, and ITT sets), Study 827

	Placebo	Humira 160/80/40 mg	Difference (Humira-placebo)	p-value
mITT (NRI)	9.3% (23/246)	16.6% (41/247)	7.3%	0.018
PP (NRI)	9.9% (21/212)	17.0% (36/212)	7.1%	0.027
ITT (LOCF)	10.6% (23/246)	18.2% (41/248)	7.6%	0.024

Adapted from Applicant's Table 35, Study 826 CSR p 224/3375
LOCF = last observation carried forward; NRI = non-responder imputation
a. p values for adalimumab versus placebo in ITT-A3 set (NRI and LOCF analyses) and placebo set from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5). For subjects in the ITT-E set, the P value to compare adalimumab 160/80/40 versus placebo is from CMH test with subjects in/not in the ITT-A3 set as the stratification factor; and the p value to compare adalimumab 80/40 versus placebo is from chi-square test (or Fisher's exact test if ≥ 20% of cells had expected cell count < 5).
b. Per the LOCF analysis, the last non-missing post-Baseline values were carried forward.

Similar to Study 826, a post-hoc sensitivity analysis using the intended FDA definition of remission was conducted. To be counted as being in remission, patients had to meet the following criteria:

a. Total Mayo score ≤2
b. Rectal bleeding subscore=0 (no bleeding)
c. Endoscopy subscore=0 (e.g., no friablility)
d. No individual subscore >1.

Subgroup Analysis

Subgroup analysis of the primary induction endpoint in Study 827 revealed that the 95% confidence interval for the difference between Humira and placebo included zero for most subgroups (p-value >0.05). Exceptions included white race, CRP <10.0 mg/L, current smoker, and use of azathioprine and 6-mercaptopurine at baseline. See Table 22 below.

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Table 22. Subgroup Analysis of Primary Induction Endpoint, Study 827

Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	(0.1%, 15.2%)
Female	10/94 (10.6%)	18/106 (17.0%)	(-3.1%, 15.8%)
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	(2.4%, 17.9%)
40-64	13/116 (11.2%)	17/105 (16.2%)	(-4.1%, 14.1%)
≥65	2/12 (16.7%)	1/7 (14.3%)	(-33.8%, 31.0%)
Race			
White	23/234 (9.8%)	38/236 (16.1%)	(0.2%, 12.3%)
Non-white	0/12 (0.0%)	3/12 (25.0%)	
Weight			
< 70 kg	7/91 (7.7%)	16/95 (16.8%)	(-0.2%, 18.5%)
≥70 kg	16/155 (10.3%)	25/153 (16.3%)	(-1.7%, 13.3%)
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	(2.0%, 18.6%)
Yes	7/101 (6.9%)	9/98 (9.2%)	(-5.3%, 9.8%)
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	(0.0%, 15.2%)
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	(-3.0%, 13.1%)
Smoker			
Ex-smoker	7/88 (8.0%)	15/94 (16.0%)	(-1.3%, 17.3%)
Smoker	2/19 (10.5%)	2/20 (10.0%)	(-19.5%, 18.5%)
Non-smoker	14/138 (10.1%)	24/134 (17.9%)	(-0.5%, 16.0%)
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	(-12.4%, 8.3%)
No	11/166 (6.6%)	29/155 (18.7%)	(4.9%, 19.3%)
Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	(3.3%, 19.5%)
No	10/106 (9.4%)	10/98 (10.2%)	(-7.4%, 8.9%)

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MAINTENANCE OF REMISSION

Study 827

Study 827 was the single study used to evaluate Humira for the indication of maintenance of remission of UC in adult patients. Efficacy data at Week 52 from Study 826 were used as supportive evidence.

In Study 827, ranked co-primary endpoint evaluation was carried out in a hierarchical fashion using a two-sided Cochran-Mantel-Haenszel (CMH test) adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 52 was tested after the Week 8 remission rate. Remission per Mayo score was defined as Mayo score (composite score based on SFS, RBS, PGA, and endoscopy) ≤ 2 with no sub-score > 1 (the same definition used for the induction indication).

For the primary analysis, the ITT population was used and missing data was imputed using a non-responder imputation (NRI). For this method, all persons with missing data at the time of the endpoint analysis were considered non-remitters. Humira 80/40mg was not tested in Study 827.

At Week 52, 17.3% of patients taking Humira were in remission compared with 8.5% of patients taking placebo, p-value 0.004.

Table 23. Rate of Maintenance of Remission, Week 52

	Placebo	Humira 160/80/40	Difference (Humira-placebo)	p-value
Remission Rate	8.5% (21/246	17.3% (43/248)	8.8%	0.004

Non-responder Imputation (NRI) of missing data

MO Comment:
A March 2010 advice letter from the FDA alerted the Applicant that the Agency felt that Study 827 was not designed to adequately evaluate the efficacy of Humira for the maintenance of remission indication. Instead, as designed, Study 827 could only evaluate induction of remission and induction of sustained clinical remission. To support a claim of maintenance of remission, patients who were in remission at Week 8 should have been re-randomized because without re-randomizing patients who are in remission, an effect on maintenance will be confounded with an effect on induction.

In addition, the number of patients with missing data at Week 52 was disproportionate among the treatment groups. More patients had missing data in the placebo group than in the Humira group (188 vs. 166, p-value=0.0193). According to the statistical reviewer, Milton Fan, this different pattern of missing data tends to bias the results in

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favor of Humira given the Applicant's *use of the non-responder imputation method where all persons with missing data are counted as not being in remission.*

6.1.5 Analysis of Secondary Endpoints(s)

Study 826
Twelve ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint. See Section 5.3.8 of this review for the complete list of secondary endpoint variables. The first ranked endpoint (clinical response per Mayo score at Week 8 in the Humira 160/80/40 mg treatment group versus placebo) had a p-value of 0.107 (statistical non-significance).

MO Comment:
None of the pre-specified secondary endpoints were met in Study 826. This, along with other statistical issues discussed in this review, brings into further question the robustness and therefore the clinical meaningfulness of the Study 826 results.

Table 24. Ranked Secondary Endpoint Results, Study 826 (ITT-A3; NRI)

	Number (%) of Subjects		
Proportion of Subjects With:[a]	**Placebo N = 130**	**Adalimumab 160/80/40 N = 130**	***P* value**[b]
1. Clinical response at Week 8	58 (44.6)	71 (54.6)	0.107
2. Mucosal healing at Week 8	54 (41.5)	61 (46.9)	0.382
3. RBS ≤ 1 at Week 8	86 (66.2)	101 (77.7)	0.038
4. PGA ≤ 1 at Week 8	61 (46.9)	78 (60.0)	0.035
5. SFS ≤ 1 at Week 8	49 (37.7)	63 (48.5)	0.080
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
6. Clinical response at Week 8	58 (44.6)	67 (51.5)	0.264
7. Mucosal healing at Week 8	54 (41.5)	49 (37.7)	0.526
8. RBS ≤ 1 at Week 8	86 (66.2)	91 (70.0)	0.506
9. PGA ≤ 1 at Week 8	61 (46.9)	70 (53.8)	0.264
10. SFS ≤ 1 at Week 8	49 (37.7)	47 (36.2)	0.797
	Placebo N = 130	**Adalimumab 160/80/40 N = 130**	
11. IBDQ response at Week 8	75 (57.7)	79 (60.8)	0.614
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
12. IBDQ response at Week 8	75 (57.7)	70 (53.8)	0.532

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore

a. Listed in rank order, as indicated by the number preceding each endpoint variable.

b. *P* value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

Copied and electronically reproduced from Applicant's Table 37, CSR, Study 826 p 223/3375

Study 827

Fifteen ranked secondary variables were tested in a hierarchical order. Statistically significant results had to be achieved for a comparison to allow evaluation of a subsequent endpoint. The first ranked secondary endpoint of sustained remission at Weeks 8 and 52 had only borderline statistical significance using the CMH test and was non-significant when the more conservative **Fisher's exact test was used.**

The first ranked secondary endpoint in Study 827 was the proportion of patients in remission at Week 8 and Week 52 (sustained remission).

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MO Comment: The sustained remission endpoint is more important than the primary maintenance endpoint because it more completely addresses the question of whether Humira works for the maintenance of remission.

In Study 827, 17.3% of Humira 160/80/40 mg patients and 4.1% of placebo patients were in remission at Week 8 and Week 52 (p-value 0.047). Further examination of these results reveals a treatment effect of only 4.4%.

Table 25. Proportion of Patients in Remission, Weeks 8 & 52, Study 827

	Humira 160/80/40	Placebo	Difference (Humira-Placebo)	p-value
Clinical Remission, Weeks 8 & 52	8.5% (21/248)	4.1% (10/246)	4.4%	0.047

P value to compare treatment groups was based on CMH test (stratification levels: prior anti-TNF versus anti-TNF-naïve).

The p-value of 0.047 only borders on statistical significance using the CMH test and does not provide reassurance that a difference in efficacy (for the maintenance of remission) actually exists given the inherent design flaws of Study 827 to assess efficacy for maintenance of remission. **See Table 25 above. Further, if Fisher's exact** test were used, the p-value would be non-significant at 0.0621.

MO Comment:
Similar to the induction results, the maintenance results are not robust and the treatment difference is small (4.4%). Although there are limitations of cross-study comparisons, the results suggest that the magnitude of the treatment effect with Humira is lower than that with Remicade. The rates of sustained remission were 20% in Remicade patients and 7% in placebo patients, resulting in a treatment difference of 13%. However, it should be noted that the ***definition of "sustained clinical remission"*** *differed between the Remicade study (ACT 1) and the Humira study (827). The* ***Remicade study (ACT 1) defined "sustained clinical remission" as clinical remission at*** *Weeks 8, 30, and 54; in contrast, the Humira study (827)* ***defined "sustained clinical remission" as clinical remission at Weeks 8 a****nd 52. [The definition of clinical remission was the same for both the Remicade study (ACT 1) and the Humira study (827); i.e., total Mayo score of ≤2 with no individual subscore >1].*

Because the first ranked secondary endpoint (sustained remission, Weeks 8 and 52) had only borderline significance and, the other secondary endpoints are viewed as exploratory and are listed in

Table 26 below and will not be further discussed in this review.

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Table 26. Ranked Secondary Endpoints, Study 827

Ranked Secondary Endpoint		Placebo N=246	Humira (160/80/40 mg) N=248	p-value
1	Sustained remission, Week 8 and Week 52	4.1% (10)	8.5% (21)	0.047
2	Response, Week 8	34.6% (85)	50.4% (125)	<0.001
3	Response, Week 52	18.3% (45)	30.2% (75)	0.002
4	Sustained Response, Week 8 and Week 52	12.2% (30)	23.8% (59)	<0.001
5	Mucosal healing, Week 8	31.7% (78)	41.1% (102)	0.032
6	Mucosal healing, Week 52	15.4% (38)	25.0% (62)	0.009
7	Sustained Mucosal healing, Week 8 and Week 52	10.6% (26)	18.5% (46)	0.013
8	Discontinued corticosteroid use before Week 52 and achieved remission, Wee5 52	5.7% (8)	13.3% (20)	0.035
9	PGA (physician's global assessment) ≤1, Week 8	37.4% (92)	46.0% (114)	0.058
10	SFS (stool frequency sub-score) ≤1, Week 8	28.5% (70)	37.9% (94)	0.028
11	RBS (rectal bleeding sub-score) ≤1, Week 8	58.1% (143)	70.2% (174)	0.006
12	Discontinued corticosteroid use ≥9 days before Week 52 and achieved remission at Week 52	5.7% (8)	13.3% (20)	0.035
13	Discontinued corticosteroid use and achieved sustained remission at both Weeks 32 and 52	1.4% (2)	10.0% (15)	0.002
14	IBDQ responders at Week 52	16.3% (40)	26.2% (65)	0.007
15	IBDQ responders at Week 8	45.5% (112)	58.1% (144)	0.006

Study 827, CSR p 354/3632

6.1.6 Other Endpoints

No other endpoints were assessed.

6.1.7 Subpopulations

Study 827 allowed entry of patients with prior use of infliximab or other anti-TNF agents. The ranked co-primary endpoint evaluation used a two-sided CMH test and adjusted for prior exposure to infliximab or other anti-TNF agents.

Sub-group analysis by prior anti-TNF use: At Week 8, a numerically higher treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use. At Week 52, a similar treatment difference was observed in the subgroup of patients with no prior anti-TNF use compared to the subgroup of patients with prior anti-TNF use. See Table 27, below.

Table 27. Remission Results, by prior anti-TNF use, Study 827

Anti-TNF stratification	Week 8				Week 52			
	Placebo	Humira 160/80/40		p-value	Placebo	Humira 160/80/40		p-value
No prior anti-TNF	11.0% (16/145)	21.3% (32/150)	10.3%	0.017	12.4% (18/145)	22.0% (33/150)	9.6%	0.029
Prior anti-TNF	6.9% (7/101)	9.2% (9/98)	2.3%	0.559	3.0% (3/101)	10.2% (10/98)	7.2%	0.039

Information from Table 22, CSR Study 827, p254/3632

MO Comment:
As discussed earlier, although there are limitations of cross-study comparisons, a substantially higher treatment difference was observed with Remicade in ACT 1 and ACT 2 compared to that observed with Humira in Studies 826 and 827. Given this information, should a TNF-naïve patient be started on Remicade, preferentially, after failing conventional therapy? These data suggest that if the response to Remicade is inadequate, there is no benefit in using Humira in these patients.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The PK assessments done in Study 827 suggest that a higher dose of Humira may show higher Week 8 remission rate. For more information, see the Clinical Pharmacology Review by Lin Zhou, PhD and Nitin Mehrotra, PhD (with FDA **Commissioner's Fellow Mi**chael Bewernitz, PhD).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Patients who lost response were allowed to dose escalate during the maintenance phase of all studies from 40 mg eow to 40 mg ew. However, only 7.4% of patients who escalated to 40 mg ew achieved clinical remission at Week 52 which suggests that there is no efficacy advantage to weekly dosing. The maintenance results are confounded by the lack of re-randomization at Week 8. For more information see the Clinical Pharmacology Review by Lin Zhou, PhD and Nitin Mehrotra PhD (with FDA **Commissioner's Fellow Mi**chael Bewernitz, PhD).

6.1.10 Additional Efficacy Issues/Analyses

Humira: A number needed to treat (NNT) analysis was performed. According to this analysis, approximately 11 to 14 patients would have to be treated with Humira in order to achieve induction of remission at Week 8 in one patient. For sustained remission, the NNT for Humira patients was approximately 23 patients compared with approximately 8 Remicade patients. See table below.

Table 28. NNT Analysis, Humira, Induction of Remission (Week 8) and Sustained Remission (Weeks 8 and 52)

	Indication	Study	Timepoint	NNT	95% CI
Humira	Induction of Remission	826	Wk 8	10.8	(5.7, 111)
		827	Wk 8	13.9	(7.6, 76.9)
	Sustained Remission	827	Wks 8 and 52	22.7	(11.5, 666.7)

Source: Milton Fan, statistical reviewer

Cross-Study Comparison with Remicade: A number needed to treat (NNT) analysis was performed for Remicade.

Table 29. NNT Analysis, Remicade Induction of Remission (Week 8)

	Indication	Study	Timepoint	NNT	95% CI
Remicade	Induction of Remission	ACT 1	Wk 8	4.2	(2.9, 7.6)
		ACT 2	Wk 8	3.5	(2.7, 5.3)
	Sustained Remission	ACT 1	Wks 8, 30, and 52	7.7	(4.6, 20.6)

Source: Milton Fan, statistical reviewer

MO Comment:
Although there are limitations of cross-study comparisons, the NNT results suggest that considerably fewer patients need to be treated with Remicade compared with Humira to achieve induction of remission and sustained remission. While exploratory, the NNT analysis further supports the conclusion that the benefits of Humira do not outweigh the risks.

For Humira, approximately 12 patients treated for 8 weeks would yield just one patient in remission. For the currently marketed Remicade, approximately 4 patients would need to be treated for 8 weeks to achieve similar results. The NNT results for the sustained remission endpoint are even more concerning and suggest that more than 20 patients would need to be exposed to Humira compared with 8 patients treated with Remicade to achieve remission in one patient.

7 Review of Safety

Safety Summary

No new safety signals were identified in review of the current Application. Known events associated with the use of Humira appear to be adequately represented in current labeling.

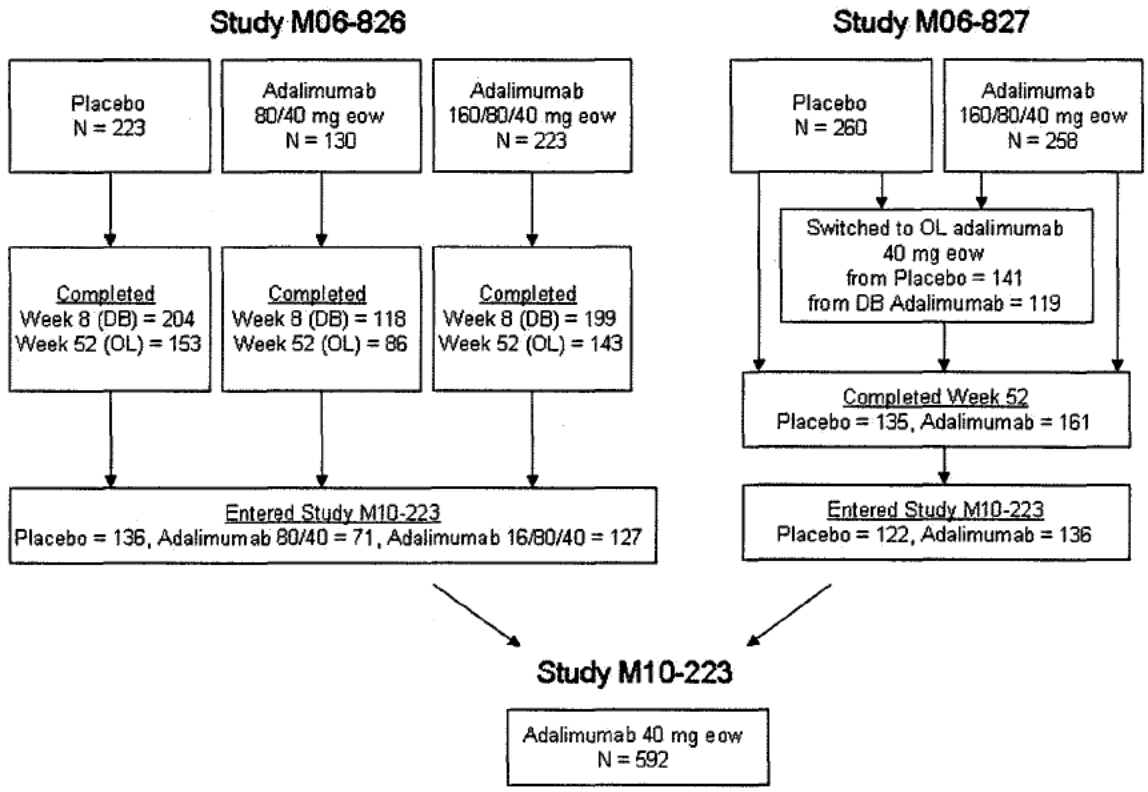
7.1 Methods

Humira was evaluated in 1,010 patients with moderately to severely active UC (Mayo score of 6 to 12) in controlled and open-label studies.

Three analysis populations were used for all analyses in the integrated safety summary: the induction set, the maintenance set, and the All Humira set. The induction set included patients enrolled in the double-blind portions of Studies 826 and 827 during Weeks 0 to 8 who received at least one dose of study drug. The maintenance set included all patients in Study 827 enrolled betweens Week 8 and Week 52 who received at least one dose of study drug (Humira or placebo). The All Humira set included all patients who received at least one dose of Humira during Study 826, 827, or 223. These sub-populations were taken from the larger Safety Population, which included all patients who received at least one dose of the study drug (Humira or placebo) and provided at least one post-baseline safety assessment.

Reference ID: 3200370

Figure 4. Safety Studies, Patient Disposition



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7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from Studies 826 and 827 (described earlier). Additionally, safety information was obtained from the ongoing Study M110-223 (Study 223). The Applicant submitted a 120-day safety update that included a data cut-off date of 31 December 2010.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 12.1.

During the studies used to investigate safety, the investigator was to monitor each patient for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the studies and at a 70-day follow-up phone call. An AE was defined as any

untoward medical occurrence in a patient enrolled in a study. The AE did not have to have a causal relationship with study drug treatment.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from three studies: Study 826, Study 827, and Study 223. See Section 7.1 for a description of how pooled data is presented in this review.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across all three studies, the mean duration of exposure to Humira was 542.5 days (range 14 to 1,475 days). Of the 1,010 patients in the All Humira Set, 60.0% (606) used Humira for greater than 12 months, 49.6% were exposed for greater than 18 months, and 35.4% were exposed for greater than 24 months. See Table 30 below.

Table 30. Extent of Exposure, All Humira Set (Months)

Months of Exposure	Humira 40 mg every week N=402	Humira 40 mg every other week N=608	All Humira N=1010
0-1	402 (100%)	608 (100%)	1010 (100%)
>1-2	402 (100%)	560 (92.1%)	962 (95.2%)
>2-12	245 (60.9%)	379 (60.5%)	606 (60.0%)
>12-24	143 (35.6%)	262 (43.1%)	405 (40.1%)
≥24-32	59 (14.7%)	138 (22.7%)	197 (19.5%)
>32-33	52 (12.9%)	121(19.9%0	173 (17.1%)
>33-36	44 (10.0)	102 (16.8)	146 (14.5)
>36-42	27 (6.7)	62 (10.2)	89 (8.8)
>46-48	2 (0.5)	6 (1.0)	8 (0.8)
>48	1 (0.2)	2 (0.3)	3 (0.3)
Mean ± SD (days)	532.2 ± 344.03	549.3 ± 396.45	542.5 ± 376.38
Median (days)	497.0	571.0	517.5
Range (days)	35-1475	14-1470	14-1475
Total number of Humira Injections			
Mean ± SD	62.1 ± 43.14	42.4 ± 28.66	50.2 ± 36.41
Median	50.0	42.5	46.0
Range	3-199	1-112	1-199

Table 5 & 6, 4-month Safety Update p 115-120/6263

7.2.2 Explorations for Dose Response

There were two induction dosing regimens—**160/80/40 mg or 80/40 mg. The higher** induction dose group was shown to have more efficacy (higher percentage of patients reaching remission as defined by the primary endpoint) than the lower dose group. There was no clear trend of higher incidence of AEs with increasing Humira dose seen in the UC studies. Specifically, only the injection site reaction preferred term showed a clear trend of increasing incidence with increasing Humira dose. .

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this BLA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see the Clinical Pharmacology Review by Lin Zhou, PhD and Nitin **Mehrotra PhD (with FDA Commissioner's** Fellow Michael Bewernitz, PhD).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for possible malignancies and infection--events known to be associated with TNF inhibitors. The studies did not reveal any new safety signals.

7.3 Major Safety Results

During studies 826, 827, and 223, approximately 84% of patients taking Humira reported at least one treatment-emergent AE. For the patients included in the induction set, the number of patients reporting AEs taking placebo and taking Humira was similar (58.0% (placebo) vs. 53.8 % (Humira 80/40 mg), 55.6% (Humira 160/80/40 mg)). The rate of treatment-related AEs was also similar between placebo and Humira patients included in the Maintenance Set (68.2% vs. 73.5%, respectively).

Table 31. Summary of Safety Results

	Induction Set			Maintenance Set		All Humira Set		
	Placebo N=483	Humira 80/40 N=130	Humira 160/80/40 N=480	Placebo N=223	Humira 160/80/40 N=234	Humira 40 mg ew N=360	Humira 40 mg eow N=635	All Humira N=1010
	n (%)							
Any Adverse Event	280 (58.0)	70 (53.8)	267 (55.6)	152 (68.2)	172 (73.5)	310 (86.1)	496 (78.1)	845 (83.7)
Any treatment-related AE[+]	112 (23.2)	28 (21.5)	110 (22.9)	48 (21.5)	72 (30.8)	165 (45.8)	254 (40.0)	419 (42.1)
Any Severe AE	41 (8.5)	9 (6.9)	35 (7.3)	16 (17.2)	24 (10.3)	83 (23.1)	140 (22.0)	223 (22.4)
Serious Adverse Event (SAE)	40 (8.3)	5 (3.8)	25 (5.2)	16 (7.2)	24 (10.3)	82 (23.1)	140 (22.0)	223 (22.4)
Discontinuation due to Adverse Event	32 (6.6)	8 (6.2)	24 (5.0)	14 (6.3)	12 (5.1)	56 (15.6)	94 (14.8)	150 (15.1)
Death	0	0	0	0	0	1 (0.3)	0	1 (0.1)
Any malignancy	2 (0.4)	0	1 (0.2)	0	1 (0.4)	1 (0.3)	9 (1.4)	10 (1.0)

[+] Any AE at least possibly related as assessed by the investigator
Source: ISS and 4 Month Safety Update Tables 15-17

7.3.1 Deaths

There was one death reported in the three studies submitted in this Application. The patient (72902) died at age 36 on Day 543 of Humira (9 days after his last dose). He was a Caucasian male randomized to Humira 160/80/40 mg in Study 827 and continued

on Humira in Study 223. During this study, the patient dose-escalated to Humira 40 ew. The patient had a non-serious event of flu syndrome, head pain, body aches, and fever 3 days prior to his death. He was found in respiratory arrest by his mother and transferred to a hospital where resuscitation efforts were unsuccessful. Autopsy revealed a bilateral adrenal hemorrhage secondary to an infectious process whose etiology could not be determined from the autopsy. The death was considered possibly related to study drug.

7.3.2 Nonfatal Serious Adverse Events

Induction Set

During the 8 week induction periods of Studies 826 and 827, a total of 610 patients were exposed to Humira. Serious adverse events (SAEs) were reported in 5 patients (3.8%) taking Humira 80/40 mg and 25 patients (5.2%) taking Humira 160/80/40 mg. In comparison, 40 patients (8.3%) in the placebo group reported an SAE. The most commonly reported SAEs were in the gastrointestinal disorders System Organ Class. In all treatment groups, the most commonly reported MedDRA preferred term was ulcerative colitis.

Table 32. Serious Adverse Events by System Organ Class, Induction Set

System Organ Class	Placebo N=483	Humira 80/40 N=130	Humira 160/80/40 N=480
Blood and lymphatic system disorders	2 (0.4)	0	2 (0.4)
Cardiac disorders	0	0	1 (0.2)
Gastrointestinal disorders	29 (6.0)	3 (2.3)	16 (3.3)
Infections and infestations	8 (1.6)	2 (1.6)	3 (0.6)
Investigations	1 (0.2)	0	
Neoplasms benign, malignant and unspecified	2 (0.4)	0	0
Nervous System Disorders		0	1 (0.2)
Psychiatric Disorders	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	1 (0.2)	0	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	3 (0.6)	0	1 (0.2)
Skin and subcutaneous tissue disorders	4 (0.8)	0	1 (0.2)
Vascular disorders	2 (0.4)	0	2 (0.4)

Source: ISS Table 25, p 49/139

Maintenance Set

Patients in the Maintenance Set were enrolled in Study 827 and received at least one dose of study drug between Weeks 8 and 52. Of these, 11 patients (4.9%) in the placebo group and 15 patients (6.4%) in the Humira group reported at least one SAE. Similar to the induction set, the most commonly reported SAE was ulcerative colitis.

Reference ID: 3200370

Other than "Gastrointestinal disorders" no other System Organ Class had more than one patient per treatment group reporting an event.

All Humira Set

Among all patients exposed to Humira during Studies 826, 827, and 223, a total of 223 patients (22.1%) reported at least one SAE. Similar to the induction and maintenance sets, the most commonly reported SAE was ulcerative colitis.

Table 33. SAEs Reported by ≥2 Patients, All Humira Set

System Organ Class Preferred Term	Humira 40 mg ew N=402	Humira 40 mg eow N=608	All Humira N=1,010
	n (%)		
Any SAE	90 (22.4)	133 (21.9)	223 (22.1)
Blood and lymphatic system d/o			
Anemia	5 (1.2)	2 (0.3)	7 (0.7)
Cardiac disorders			
Coronary artery disease	1 (0.2)	2 (0.3)	3 (.03)
Gastrointestinal disorders			
Abdominal pain	1 (0.2)	3 (0.5)	4 (0.4)
Colitis	2 (0.5)	1 (0.2)	3 (0.3)
Ulcerative colitis	44 (10.9)	51 (88.4)	95 (9.4)
Crohn's disease	**2 (0.5)**	**0**	**2 (0.2)**
Gastrointestinal dysplasia	0	2 (0.3)	2 (0.2)
Inguinal hernia	2 (0.5)	1 (0.2)	3 (0.3)
Large intestine perforation	0	2 (0.3)	2 (0.2)
Peritonitis	0	2 (0.3)	2 (0.2)
Rectal hemorrhage	0	2 (0.3)	2 (0.2)
Small intestinal obstruction	1 (0.2)	1 (0.2)	2 (0.2)
General disorders and administration site conditions			
Noncardiac chest pain	1 (0.2)	1 (0.2)	2 (0.2)
Hepatobiliary disorders			
Cholelithiasis	1 (0.2)	1 (0.2)	2 (0.2)
Infections and infestations			
Abdominal abscess	0	3 90.5)	3 (0.3)
Anal abscess	0	4 (0.7)	4 (0.4)
Appendicitis	3 (0.7)	5 (0.8)	8 (0.8)
Cytomegalovirus colitis	1 (0.2)	1 (0.2)	2 (0.2)
Herpes zoster	1 (0.2)	2 (0.3)	3 (0.3)
Lobar pneumonia	3 (0.7)	1 (0.2)	4 (0.4)
Perirectal abscess	2 (0.5)	0	2 (0.2)
Respiratory tract infection	1 (0.2)	1 (0.2)	2 (0.2)
Investigations			
Weight decreased	1 (0.2)	1 (0.2)	2 (0.2)
Musculoskeletal and connective tissue d/o			
Arthralgia	2 (0.5)	0	2 (0.2)
Backpain	0	2 (0.3)	2 (0.2)
Intervertebral disc protrusion	0	2 (0.3)	2 (0.2)
Osteoarthritis	0	4 (0.7)	4 (0.4)
Neoplasms benign, malignant, and unspecified			
B-cell lymphoma	1 (0.2)	2 (0.3)	3 (.3)
Uterine leiomyoma	1 (0.2)	1 (0.2)	2 (.2)
Renal and urinary disorder			
Nephrolithiasis	0	2 (0.3)	2 (0.2)
Renal failure acute	2 (0.5)	0	2 (0.2)
Respiratory, thoracic, and mediastinal d/o			
Pulmonary embolism	1 (0.2)	1 (.2)	2 (.2)
Surgical and medical procedures			
Abortion induced	0	3 (0.5)	3 (0.3)
Vascular disorders			
Deep vein thrombosis	3 (0.7)	2 (0.3)	5 (.5)

4-Month Safety Update p.189-191, Table 24

7.3.3 Dropouts and/or Discontinuations

Induction Set

Overall, 31 (5.1%) patients taking Humira and 32 (6.6%) of placebo patients reported adverse events that led to discontinuation from the study. The most commonly reported AE leading to discontinuation in both treatment groups was ulcerative colitis. No other preferred term was reported as the adverse event leading to discontinuation by more than one patient in each treatment group.

Maintenance Set

Results were similar to the induction set.

All Humira Set

Among all patients exposed to Humira, 180 (17.8%) reported AEs leading to discontinuation. Preferred terms reported by more than one patient include ulcerative colitis (10%), colitis (1.0%), gastrointestinal **dysplasia (0.5%), Crohn's disease (0.2%),** and injection site reaction (0.2%). All other AEs leading to discontuation were reported by only one patient.

7.3.4 Significant Adverse Events

Significant Adverse Events for Humira include those described in the current labeling in Section 5 WARNINGS AND PRECAUTIONS. Those events listed in current labeling are discussed below.

For the adverse events below, only results from the All Humira Set will be described as these adverse events are already known to be associated with the use of Humira and comparison with placebo rates would not provide additional information.

Serious Infections

A total of 53 patients (5.2%) taking Humira during Studies 826, 827, and 223 reported treatment-emergent serious infections. The most common serious infection was appendicitis (0.8%) followed by pneumonia (0.5%). There was one case of pulmonary tuberculosis (TB) reported during the open-label extension study. The patient who acquired TB during the study was a 25 year old, white male. Symptoms of TB started on study Day 650 and the event was considered resolved on study Day 767. The patients discontinued from the study due to this event.

Malignancies

A total of 15 patients (1.5%) taking Humira were diagnosed with malignancies during Studies 826, 827, and 223. No cases of colon cancer were reported in any patient taking Humira. And no malignancies were identified in any of the three patients who were erroneously enrolled in the study with evidence of dysplasia seen during screening colonoscopy with biopsy.

A 54 year-old, white male patient taking Humira was diagnosed with both basal cell and squamous cell carcinoma of the skin. The cancers were both diagnosed on Study Day 696 of the open-label extension study (223) and the events were considered resolved on Study day 882. The patient did not discontinue from the study for these events.

Table 34. Treatment-Emergent Malignancies (All Humira Set)

MedDRA Preferred Term	All Humira N=1,010
	n (%)
Any malignancy	15 (1.5)
B-cell lymphoma	3 (0.3)
Basal cell carcinoma	2 (0.2)
Squamous cell carcinoma of skin	2 (0.2)
Breast cancer	1 (<0.1)
Breast cancer in situ	1 (<0.1)
Gastric cancer	1 (<0.1)
Malignant melanoma	1 (<0.1)
Spindle cell sarcoma	1 (<0.1)
Squamous cell carcinoma	1 (<0.1)
Bladder cancer	1 (<0.1)
Cervix carcinoma stage	1 (<0.1)
Gallbladder cancer	1 (<0.1)

Source: Applicant's Table 33, 4-month Safety update p 232/6263

Hypersensitivity Reactions
A total of 11 patients (1.1%) taking Humira were diagnosed with allergic reactions during Studies 826, 827, and 223. Two patients (0.2%) reported drug hypersensitivity reactions, three patients (0.3%) reported facial edema, and six patients (0.6%) reported urticaria.

A 36 year-old, Asian female reported a hypersensitivity drug reaction. She reported an itchy, pimply, red rash on her neck, eyebrows, chin, chest, and upper legs. She experienced this reaction on study Day 144. The event was considered resolved on Study Day 177. She was treated with a steroid cream and Benadryl. The patient discontinued from the study due to this reaction.

A 29 year-old, white female experienced a hypersensitivity drug reaction. On study Day 30 the patient reported multiple bullae on her body, mostly on her chest and back. The patient discontinued the study drug and this severe event was considered resolved on Study Day 162.

Hepatitis B Virus Reactivation
There were no cases of hepatitis B Virus reactivation reported during the studies submitted in support of this Application.

Neurologic Reactions
There were no cases of neurologic reactions reported during the studies submitted in support of this Application (including new cases of demyelinating disease).

Hematologic Reactions
Hematologic adverse events occurred in 21 patients (2.1%) receiving Humira in the studies submitted with the current sBLA. Of these, only one event (an episode of leukopenia) was considered a serious adverse event. This SAE occurred in a 35 year-old, black male on study Day 26. The event was considered resolved on study Day 31. The patient was hospitalized and underwent a work-up to rule out infection. The patient was on concomitant 6-MP. The patient discontinued the study drug for 9 days and then continued on in the study.

Of the 21 patients reporting hematologic adverse events, 19 (1.9%) were receiving concomitant AZA and/or 6-MP at baseline.

Table 35. Humira Patients reporting Hematologic Adverse Events

MedDRA Preferred Term	All Humira N=1,010
	n (%)
Any hematologic AE	20 (2.0)
Leukopenia	16 (1.6)
Neutropenia	4 (0.4)
Thrombocytopenia	1 (0.1)

Source: 4-mo Safety Update Table 40, p259/6263

CHF
Two patients taking Humira reported CHF-related AEs. A 52 year-old, black female reported pulmonary congestion on study Day 198. A 40 year-old, white male was diagnosed with right ventricular failure and overload on study Day 73. Neither event resulted in the hospitalization of the patient.

7.3.5 Submission Specific Primary Safety Concerns

See Section 7.3.4 above for adverse events in the current Humira WARNINGS AND PRECAUTIONS section of the label.

Humira is administered by subcutaneous injection; therefore, the frequency of injection site reactions is an additional submission specific primary safety concern. For this section, the placebo reaction rates will be listed as both placebo and Humira patients were given subcutaneous injections. The difference between the placebo and Humira injection site reactions can be attributed to the Humira drug product.

Induction Set
During the 8 week induction periods of Studies 826 and 827, injection site reactions were reported in15 placebo patients (3.1%) and 37 Humira patients (6.1%), p=0.022. The most common injection site reactions in placebo patients were pain (2.3%), erythema (0.4%), and unspecified injection site reaction (0.4%). The most common

injection site reactions in patients taking Humira were pain (2.3%), erythema (1.8%), pruritus (1.1%), and general injection site reactions (1.1%).

Maintenance Set
Of patients in the Maintenance Set (i.e., received blinded treatment from Week 8 through Week 52 in Study 827), 11 patients (1.3%) in the placebo group and 15 patients (6.8%) reported injection site reactions (p=0.004).

All Humira Set
In the All Humira Set, 105 patients (10.4%) of patients reported injection site reactions. In patients taking Humira, three events were recorded as severe. A 41 year old, white male reported burning upon injection and permanently discontinued the study drug. A 36 year old, white male reported itching, swelling, redness, and pain and permanently discontinued the study drug. A 38 year-old, white male reported a severe event of post-injection itching.

The most commonly reported injection site reactions in patients taking Humira were erythema, pain, pruritis, and general injection site reaction. See Table 36 below for details.

Table 36. Injection Site Reactions, All Humira Set

Safety Update		
Adalimumab 40 mg ew N = 402	**Adalimumab 40 mg eow N = 608**	**All Adalimumab N = 1010**
43 (10.7)	62 (10.2)	105 (10.4)
15 (3.7)	18 (3.0)	33 (3.3)
4 (1.0)	6 (1.0)	10 (1.0)
2 (0.5)	1 (0.2)	3 (0.3)
1 (0.2)	3 (0.5)	4 (0.4)
0	1 (0.2)	1 (< 0.1)
1 (0.2)	0	1 (< 0.1)
0	2 (0.3)	2 (0.2)
4 (1.0)	15 (2.5)	19 (1.9)
8 (2.0)	11 (1.8)	19 (1.9)
4 (1.0)	2 (0.3)	6 (0.6)
18 (4.5)	19 (3.1)	37 (3.7)
4 (1.0)	7 (1.2)	11 (1.1)
1 (0.2)	2 (0.3)	3 (0.3)

Copied and electronically reproduced from Applicant's 4-mo safety update Table 35 p 238/6263

7.4 Supportive Safety Results

N/A

7.4.1 Common Adverse Events

Induction Set
During the randomized, double-blind, eight-week induction period of studies 826 and 827, a total of 282 placebo patients (58.4%) and 335 Humira patients (54.9%) reported adverse events. The most common adverse events reported by patients in any treatment group were ulcerative colitis, headache, and nasopharyngitis. See Table 37 below for the most common adverse events reported during the induction period.

Table 37. TEAEs Reported by ≥2% of Patients, Induction Set

MedDRA System Organ Class Preferred Terms	**Placebo N=483**	**Humira 80/40 N=130**	**Humira 160/80/40 N=480**	**Total Humira N=610**
	n(%)			
Blood and lymphatic system disorders				
Anemia	14 (2.9)	2 (1.5)	9 (1.9)	11(1.8)
Gastrointestinal Disorders				
Abdominal Pain	15 (3.1)	3 (2.3)	6 (1.3)	9 (1.5)
Abdominal tenderness	5 (1.0)	3 (2.3)	3 (0.6)	6 (1.0)
Colitis Ulcerative	59 (12.2)	10 (7.7)	35 97.3)	45 (7.4)
Dyspepsia	6 (1.2)	3 (2.3)	8 (1.7)	11 (1.8)
Nausea	16 (3.3)	4 (3.1)	10 (2.1)	14 (2.3)
Toothache	0	3 (2.3)	2 (0.4)	5 (0.8)
General Disorders and Administration Site Conditions				
Fatigue	12 (2.5)	2 (1.5)	18 (3.8)	20 (3.3)
Influenza like illness	10 (2.1)	2 (1.5)	1 (0.2)	3 (0.5)
Injection site pain	11 (2.3)	2 (1.5)	12 (2.5)	14 (2.3)
Pyrexia	14 (2.9)	3 (2.3)	8 (1.7)	11 (1.8)
Infections and Infestations				
Influenza	8 (1.7)	3 (2.3)	3 (0.6)	6 (1.0)
Nasopharyngitis	23 (4.8)	6 (4.6)	26 (5.4)	32 (5.2)
Upper Respiratory Infection	12 (2.5)	6 (4.6)	5 (1.0)	11 (1.8)
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	9 (1.9)	5 (3.8)	10 (2.1)	15 (2.5)
Nervous System Disorders				
Headache	42 (8.7)	9 (6.9)	20 (4.2)	29 (4.8)
Psychiatric Disorders				
Insomnia	10 (2.1)	1 (0.8)	5 (1.0)	6 (1.0)
Skin and subcutaneous Tissue Disorders				
Acne	6 (1.2)	3 (2.3)	9 (1.9)	12 (2.0)
Erythema	2 (0.4)	3 (2.3)	8 (1.7)	11 (1.8)
Rash	5 (1.0)	5 (3.8)	4 (0.8)	9 (1.5)

Adapted from Applicant's Table 42, ISS p 203-204/5677

Maintenance Set

Of patients in the Maintenance Set (i.e., received blinded treatment from Week 8 through Week 52 in Study 827), 152 (68.2%) of placebo patients and 172 (73.5%) of Humira patients reported an AE. The most commonly reported AE was ulcerative colitis. Other common AES are in the current label. See Table 38 below.

Table 38. Common AEs, Maintenance Set

MedDRA Preferred Term	Placebo N=223	Humira 160/80/40 N=234
	N (%)	
Any Adverse Event	152 (68.2)	172 (73.5)
Colitis ulcerative	37 (16.6)	39 (16.7)
Nasopharyngitis	11 (4.9)	26 (11.1)
Abdominal pain	12 (5.4)	18 (7.7)
Arthralgia	9 (4.0)	17 (7.3)
Headache	15 (6.7)	11 (4.7)
Nausea	12 (5.4)	9 (3.8)

Source: Table 16, ISS

All Humira Set

Overall, 845 patients (83.7%) reported at least one adverse event while taking Humira. The most common AEs reported were ulcerative colitis (31.8%), nasopharyngitis (16.7%), and arthralgia (10.4%). See Table 1 below.

Table 39. Common AEs, All Humira Set

MedDRA System Organ Class Preferred Terms	
	n (%)
Blood and lymphatic system disorders	
Anemia	61 (6.0%)
Gastrointestinal Disorders	
Abdominal Pain	70 (6.9%)
Colitis Ulcerative	321 (31.8%)
Nausea	73 (7.2%)
General Disorders and Administration Site Conditions	
Fatigue	79 (7.8%)
Pyrexia	62 (6.1%)
Infections and Infestations	
Nasopharyngitis	169 (16.7%)
Upper Respiratory TractInfection	83 (8.2%)
Sinusitis	59 (5.8%)
Bronchitis	50 (5.0)
Musculoskeletal And Connective Tissue Disorders	
Arthralgia	105 (10.4%)
Back Pain	56 (5.5%)
Nervous System Disorders	
Headache	98 (9.7%)
Respiratory Tract Disorders	
Cough	63 (6.2%)
Oropharyngeal Pain	58 (5.7%)
Skin and subcutaneous Tissue Disorders	
Rash	62 (6.1%)

Source: Table 20, ISS

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinically significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters. No clinically important findings were seen that have not been described in current labeling.

7.4.3 Vital Signs

Vital sign trends were reviewed. No clinically important findings were seen.

7.4.4 Electrocardiograms (ECGs)

Humira is an approved product with no known effects on ECG findings. ECG data was recorded at screening and not repeated.

Reference ID: 3200370

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

The assessment of immunogenicity was not adequate in the current submission. The majority of patients (81.2%) had no immunogenicity data available because high Humira concentrations (≥2 mcg/mL) made it impossible to assess antibody status.

7.5 Other Safety Explorations

No other safety explorations were performed. No new non-clinical safety studies were conducted in support of this application.

7.5.1 Dose Dependency for Adverse Events

See Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

No particular explorations for drug-demographic safety interactions were conducted.

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were explored in this supplement.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Humira product label.

7.6.2 Human Reproduction and Pregnancy Data

There is no new information on pregnancy, use in labor and delivery, or lactation. Current labeling addresses these areas. Humira is pregnancy category B and should be used during pregnancy only if clearly needed. To monitor outcomes of pregnancy women, a pregnancy registry has been established.

7.6.3 Pediatrics and Assessment of Effects on Growth

Humira is currently indicated only for adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose reported in the UC Humira.

Current Humira labeling:
10 OVERDOSAGE

> Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

Humira has low abuse potential.

7.7 Additional Submissions / Safety Issues

On September 7, 2011 the FDA released a Drug Safety Communication (DSC) to inform health care providers about the updated *Boxed Warning* for the entire class of Tumor Necrosis Factor-alpha (TNFα) blockers. The updated warnings concern the risk of infection from Legionella and Listeria associated with the use of TNF blockers.

8 Postmarket Experience

See Current Lialda label.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

N/A

9.3 Advisory Committee Meeting

N/A

Appendix A

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore.

Stool frequency subscore* 0 = Normal number of stools for this subject 1 = 1-2 stools more than normal 2 = 3-4 stools more than normal 3 = 5 or more stools more than normal * Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.
Rectal bleeding subscore** 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passed ** The daily bleeding score represents the most severe bleeding of the day.
Endoscopy subscore: Findings of flexible sigmoidoscopy 0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's Global Assessment subscore*** 0 = Normal (subscores are 0) 1 = Mild disease (subscores are mostly 1's) 2 = Moderate disease (subscores are 1 to 2) 3 = Severe disease (subscores are 2 to 3) *** The physician's global assessment acknowledges the three other subscores, the subject's daily record of abdominal discomfort and functional assessment, and other observations such as physical findings, and the subject's performance status.

Adapted with permission from KW Schroeder.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.

Reference ID: 3200370

Appendix B

To enroll in Study 827 with prior exposure to infliximab or any anti-TNF agent must have met one of the following two conditions:

Loss of Response

The investigator judges the subject to have responded to the anti-TNF agent in the past and demonstrated a loss of response by meeting one of the following criteria after the last dose (Note: a subject with prior infliximab exposure must have responded to a dose of ≥ 5 mg/kg and demonstrated loss of response ≥ 14 days after they received at least 2 subsequent and sequential doses of ≥ 5 mg/kg at an interval not exceeding 56 days).

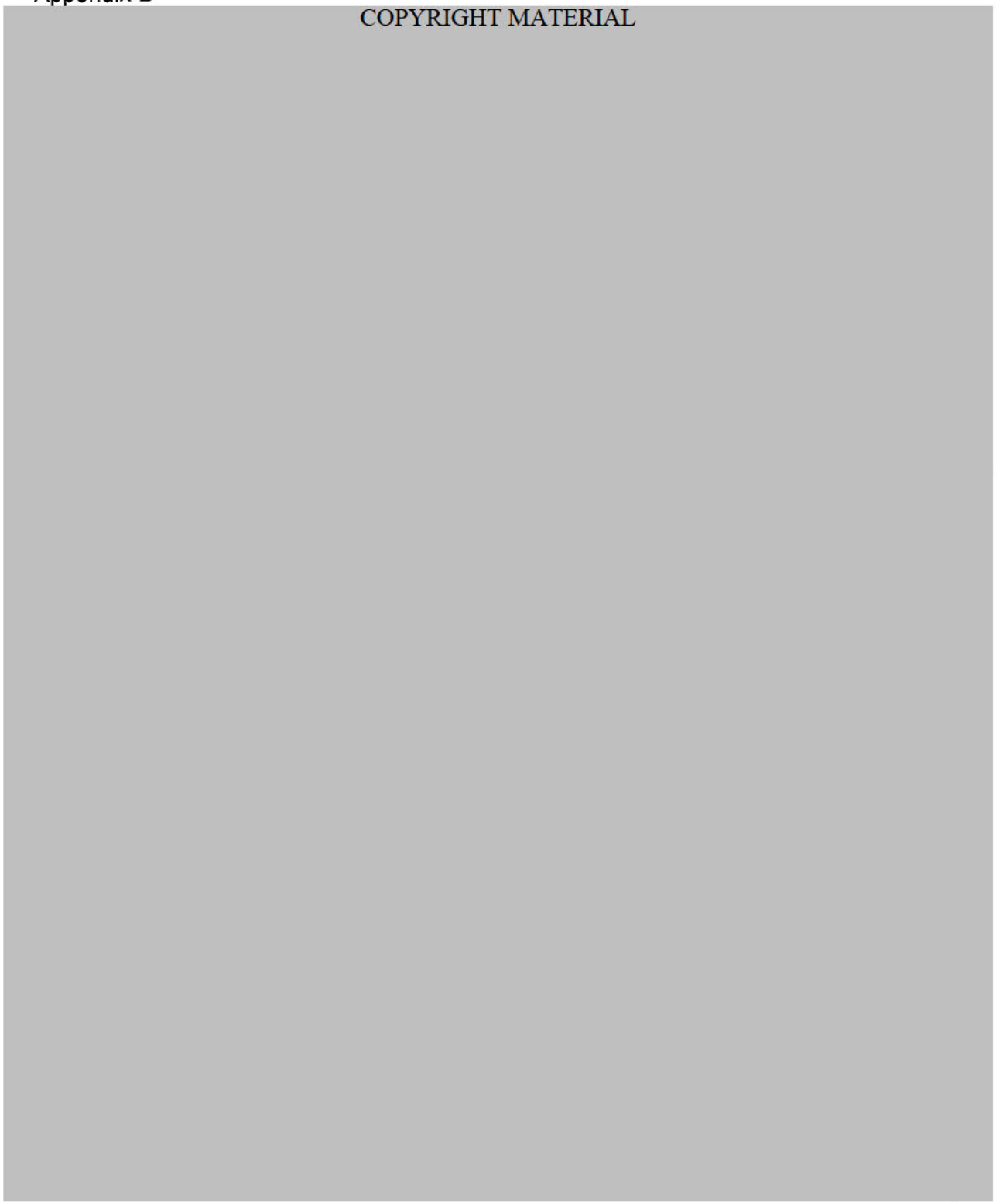
- Experienced an overall lack of improvement
- Experienced a worsening of the following, but not inclusive, UC related signs/symptoms:
  - Stool frequency
  - Abdominal pain
  - Rectal bleeding
  - Fever
  - Weight loss

Intolerance to Anti-TNF agent

A subject is defined as intolerant when, in the opinion of the investigator, therapy was discontinued as a result of a significant acute or delayed reaction to the medication. A reaction is considered significant if at least one of the clinical characteristics listed below is reported by history and is documented in progress notes or other source documents.

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Appendix B



Appendix C

SF-36® Health Survey

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Table 20. Treatment-Emergent Adverse Events Reported by >= 2% of Subjects in All Adalimumab Group (All Adalimumab Set)

MedDRA System Organ Class Preferred Term	ISS All Adalimumab N = 995 PYs = 1041.02		Safety Update All Adalimumab N = 1010 PYs = 1500.15	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
Any adverse event	806 (81.0)	5245 (503.83)	845 (83.7)	6338 (422.49)
Blood and lymphatic system disorders				
Anaemia	55 (5.5)	63 (6.05)	61 (6.0)	77 (5.13)
Iron deficiency anaemia	19 (1.9)	19 (1.83)	22 (2.2)	22 (1.47)
Endocrine disorders				
Cushingoid	13 (1.3)	13 (1.25)	14 (1.4)	14 (0.93)
Gastrointestinal disorders				
Abdominal pain	62 (6.2)	75 (7.20)	70 (6.9)	91 (6.07)
Abdominal pain lower	12 (1.2)	16 (1.54)	16 (1.6)	22 (1.47)
Abdominal pain upper	24 (2.4)	25 (2.40)	28 (2.8)	29 (1.93)
Abdominal tenderness	23 (2.3)	33 (3.17)	26 (2.6)	36 (2.40)
Colitis	22 (2.2)	41 (3.94)	26 (2.6)	45 (3.00)
Colitis ulcerative	263 (26.4)	353 (33.91)	321 (31.8)	443 (29.53)
Constipation	--	--	20 (2.0)	21 (1.40)
Diarrhoea	29 (2.9)	43 (4.13)	42 (4.2)	62 (4.13)
Dyspepsia	30 (3.0)	33 (3.17)	34 (3.4)	37 (2.47)
Flatulence	22 (2.2)	29 (2.79)	25 (2.5)	34 (2.27)
Gastrooesophageal reflux disease	--	--	20 (2.0)	22 (1.47)
Haemorrhoids	26 (2.6)	28 (2.69)	32 (3.2)	36 (2.40)
Nausea	63 (6.3)	80 (7.68)	73 (7.2)	92 (6.13)
Vomiting	29 (2.9)	39 (3.75)	32 (3.2)	42 (2.80)
General disorders and administration site conditions				
Fatigue	70 (7.0)	78 (7.49)	79 (7.8)	90 (6.00)
Injection site erythema	31 (3.1)	48 (4.61)	33 (3.3)	50 (3.33)
Injection site reaction	37 (3.7)	62 (5.96)	37 (3.7)	63 (4.20)

Reference ID: 3200370

Table 20. Treatment-Emergent Adverse Events Reported by >= 2% of Subjects in All Adalimumab Group (All Adalimumab Set) (Continued)

MedDRA System Organ Class Preferred Term	ISS All Adalimumab N = 995 PYs = 1041.02		Safety Update All Adalimumab N = 1010 PYs = 1500.15	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
General disorders and administration site conditions (continued)				
Oedema peripheral	29 (2.9)	35 (3.36)	36 (3.6)	41 (2.73)
Pyrexia	56 (5.6)	67 (6.44)	62 (6.1)	74 (4.93)
Infections and infestations				
Bronchitis	37 (3.7)	46 (4.42)	50 (5.0)	60 (4.00)
Gastroenteritis	34 (3.4)	38 (3.65)	36 (3.6)	40 (2.67)
Influenza	32 (3.2)	44 (4.23)	42 (4.2)	56 (3.73)
Nasopharyngitis	139 (14.0)	217 (20.84)	169 (16.7)	286 (19.06)
Oral herpes	25 (2.5)	34 (3.27)	28 (2.8)	43 (2.87)
Pharyngitis	24 (2.4)	31 (2.98)	27 (2.7)	36 (2.40)
Sinusitis	45 (4.5)	63 (6.05)	59 (5.8)	86 (5.73)
Upper respiratory tract infection	71 (7.1)	104 (9.99)	83 (8.2)	133 (8.87)
Urinary tract infection	31 (3.1)	36 (3.46)	38 (3.8)	52 (3.47)
Viral infection	24 (2.4)	30 (2.88)	29 (2.9)	36 (2.40)
Injury, poisoning and procedural complications				
Contusion	18 (1.8)	19 (1.83)	20 (2.0)	23 (1.53)
Musculoskeletal and connective tissue disorders				
Arthralgia	91 (9.1)	116 (11.14)	105 (10.4)	141 (9.40)
Back pain	49 (4.9)	74 (7.11)	56 (5.5)	87 (5.80)
Musculoskeletal pain	25 (2.5)	25 (2.40)	31 (3.1)	31 (2.07)
Myalgia	26 (2.6)	27 (2.59)	29 (2.9)	31 (2.07)
Pain in extremity	23 (2.3)	25 (2.40)	29 (2.9)	31 (2.07)

Reference ID: 3200370

Table 20. Treatment-Emergent Adverse Events Reported by >= 2% of Subjects in All Adalimumab Group (All Adalimumab Set) (Continued)

MedDRA System Organ Class Preferred Term	ISS All Adalimumab N = 995 PYs = 1041.02		Safety Update All Adalimumab N = 1010 PYs = 1500.15	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
Nervous system disorders				
Dizziness	25 (2.5)	29 (2.79)	27 (2.7)	33 (2.20)
Headache	91 (9.1)	169 (16.23)	98 (9.7)	183 (12.20)
Psychiatric disorders				
Anxiety	21 (2.1)	23 (2.21)	28 (2.8)	30 (2.00)
Depression	--	--	23 (2.3)	24 (1.60)
Insomnia	25 (2.5)	30 (2.88)	34 (3.4)	40 (2.67)
Respiratory, thoracic and mediastinal disorders				
Cough	52 (5.2)	58 (5.57)	63 (6.2)	70 (4.67)
Nasal congestion	20 (2.0)	28 (2.69)	22 (2.2)	30 (2.00)
Oropharyngeal pain	48 (4.8)	54 (5.19)	58 (5.7)	65 (4.33)
Skin and subcutaneous tissue disorders				
Acne	31 (3.1)	37 (3.55)	33 (3.3)	38 (2.53)
Alopecia	22 (2.2)	22 (2.11)	25 (2.5)	25 (1.67)
Dry skin	31 (3.1)	33 (3.17)	35 (3.5)	38 (2.53)
Eczema	20 (2.0)	26 (2.50)	22 (2.2)	29 (1.93)
Erythema	32 (3.2)	39 (3.75)	36 (3.6)	42 (2.80)
Pruritus	42 (4.2)	53 (5.09)	47 (4.7)	60 (4.00)
Rash	52 (5.2)	66 (6.34)	62 (6.1)	78 (5.20)
Vascular disorders				
Hypertension	33 (3.3)	37 (3.55)	40 (4.0)	43 (2.87)

ew = subjects who switched to every week dosing; eow = subjects who received treatment every other week only; E/100 PY = events per 100 patient-years; PY = patient-years

Note: Treatment-emergent defined as any event with onset or worsening at or after the first dose of adalimumab treatment and up to 70 days after the last study drug injection or until the data cut-off date in Study M10-223, whichever is the earliest.

Reference ID: 3200370

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: sBLA 125,057/232 **Applicant:** Abbot Laboratories **Stamp Date:** 25 Jan 2011

Drug Name: Humira® (adalimumab) **NDA/BLA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study M06-827 See full description below. The PK and immunogenicity of adalimumab following subcutaneous administration was evaluated in UC patients. Additionally, the following studies evaluated PK in patients with Crohn's disease—M02-403, M04-691, and M02-433.	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3200370

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Study M06-826 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis. • 160/80/40, 80/40 dosing groups • 576 safety pts, 575 ITT-everyone, 390 ITT-A3 • 1° efficacy endpoint- proportion of ITT-A3 pts in remission at Week 8 • OL extension to 52 weeks Pivotal Study #2 Study M06-827 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis. • 160/80/40 vs. placebo • 518 safety pts • Co-primary endpoints: proportion of pts in remission at Week 8 (1), Week 52 (2) Indication: Reducing signs and symptoms , and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

Reference ID: 3200370

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3200370

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Our review of safety must include enough data to develop as complete a profile of the safety of Lialda as possible. Long-term Safety Study M223 provides important information; however, the interim results were provided only until December 31, 2009. The supplement was not submitted January 25, 2011. Please provide Study M223 results to at least 3 months prior to the date of submission. Please submit this information as soon as possible.

Aisha Peterson Johnson — 3/18/2011
Reviewing Medical Officer — Date

Anil Rajpal — 3/25/2011
Clinical Team Leader — Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3200370

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

CHEMISTRY REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: October 19, 2011

To: File for STN: 125057/232 (sBLA)

RPM: Kevin Burgin, ODEIII/DGP

From: Jun Park, Ph.D., Product Reviewer, DMA/OBP/CDER, HFD-123 11-15-2011

Through: Ruth Cordoba-Rodriguez, Ph.D., Team Leader, DMA/OBP/CDER 11/15/11
Patrick Swann, Ph.D., Division Deputy Director, DMA/OBP/CDER 11-16-11

Subject: New indication for adult patients with moderately to severely active ulcerative colitis

Applicant: Abbott Laboratories

Product: Humira® (adalimumab)

Supplement Receipt Date: January 25, 2011

Review Recommendation: Approval from CMC perspective.

Summary:
The purpose of this efficacy supplement is to propose a new indication for adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

All quality information resides in file under BLA 125057. However, Abbott has noted in the responses to the May 23, 2011 information request (IR) that samples from Study M06-827 were assayed for serum anti-adalimumab antibody (AAA) using a new immunogenicity method, while samples from Studies M02-403, M04-691 and M02-433 were measured for serum AAA using the original immunogenicity method approved under the original BLA.

The sponsor has developed a new immunogenicity method (improved and final new method in Table 1). The ELISA assay format was not changed significantly in comparison to that of the original assay. Differences between the three methods are summarized in Table 1.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Division of Monoclonal Antibodies
Rockville, MD 20852
Tel. 301-827-0850

Memorandum of Review

Date: March 22, 2011

To: File for STN: 125057/232 (sBLA)

RPM: Kevin Burgin, ODEIII/DGP

From: Jun Park, Ph.D., Product Reviewer, DMA/OBP/CDER, HFD-123 5-9-2011

Through: Ruth Cordoba-Rodriguez, Ph.D., Team Leader, DMA/OBP/CDER 5-9-2011
Patrick Swann, Ph.D., Division Deputy Director, DMA/OBP/CDER 5-11-11

Subject: New indication for adult patients with moderately to severely active ulcerative colitis

Applicant: Abbott Laboratories

Product: Humira® (adalimumab)

Supplement Receipt Date: January 25, 2011

Review Recommendation: Approval from CMC perspective.

Summary:
The purpose of this efficacy supplement is to propose a new indication for adalimumab; for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

All quality information resides in file under BLA 125057. In addition, Abbott noted in the submission that the validated immunogenicity assay approved under the BLA was used for the evaluation of anti-adalimumab antibody (ADA). Therefore, no CMC issues were identified.

This supplement is recommended for approval from the CMC perspective.

complete response letter. Therefore, the following text should be included in the complete response letter.

> The immunogenicity assay was not adequate. Develop, qualify and implement an improved validated anti-adalimumab antibody (AAA) assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling. Until assays have been developed and validated, patients samples collected from clinical studies should be banked under appropriate storage conditions.

It is noted in the submission that Abbott Laboratories claims categorical exclusion from the environmental assessment for this supplemental Biological License Application (sBLA) in accordance with 21 CFR 25.31(c). To Abbott's knowledge, no extraordinary circumstances exist to indicate that action under this sBLA will significantly affect the quality of the human environment.

9 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

STATISTICAL REVIEW(S)

Statistical Team Leader Memorandum

Submission: BLA 125057/232
Product: Humira (adalimumab)
Sponsor: Abbot Laboratories
Indication: Induction and maintenance of remission of ulcerative colitis
Medical Div: DGIEP

Reference: Statistical Review and Evaluation dated September 24, 2012.

The purpose of this memorandum is to summarize conclusions regarding the statistical issues discussed in the primary reviewer's evaluation of the sponsor's complete response submitted March 30, 2012.

Induction of remission at 8 weeks

Studies 826 and 827 each showed a treatment effect that was statistically significant by pre-specified analysis criteria. It is important to recognize that the primary results were replicated in both studies (similar induction rates were shown between studies among patients with no previous UC therapy). Independent substantiation of a treatment effect does not have to be shown in identically designed studies. However, an important shortcoming of study 826 was its failure to show statistical significance for the secondary endpoints.

The issues raised by the reviewer regarding alternative efficacy analyses of study 826 are much less of a concern than would be the case if there were only a single study involved. The reviewer correctly notes that study 826 was essentially underpowered. Because of the smaller sample size compared to study 827, the relatively small effect size, and the discrete nature of the data, the sensitivity of the p-value to a single patient's hypothetical change in classification status or to the use of an exact test of proportions is not an unexpected result nor one that should necessarily have been a significant review issue. Moreover, the assumptions underlying the sponsor's use of the Chi-square test statistic for study 826 are defensible, and the proper p-value for the primary comparison should be based on that analysis.

The reviewer's and sponsor's analyses adjusting for Mayo score at baseline are problematic since such analyses are driven by the observed data, and p-values are not strictly interpretable. The alternative methods to adjust the analyses presented by the sponsor seem reasonable, and there are many such methods that could have been applied. However, baseline imbalances are always possible in a randomized trial and given an appropriate randomization method, should not invalidate the pre-specified analysis results.

The sponsor's re-submission provided additional data and analyses of the 8 week induction endpoint for both studies and these results are consistent with the treatment effects observed in the primary analysis populations. Some of these supplemental analyses were in fact pre-specified prior to unblinding (see review, Section 3.1.1.1).

Section 3.1.1.2 of the review discusses the sponsor's integrated analysis of subgroup effects which showed numerically greater proportions of remitters for adalimumab across each subgroup. These results are exploratory as the primary reviewer noted; however, the data trend in a direction favorable to treatment.

Sustained remission

The interpretation of the results from Study 827 at week 52 is a concern since many subjects terminated after week 8. (See review, Section 3.1.1.3.) However it should be recognized that only about 20% of subjects in each group discontinued study enrollment during the double blind period, while an additional 55% (placebo) and 47% (adalimumab) moved to open-label treatment because they failed to maintain clinical response based on their partial Mayo scores. As pre-specified, all these subjects were considered treatment failures. A key assumption is clinical: Had these subjects remained in the study, they would not have been in remission at week 52.

The reviewer noted that non-responder imputation generally would bias results in favor of treatment when there are more drop-outs in the placebo arm. This may be true, but the bias is not measurable nor is it clear that it would be large enough to substantially alter the observed treatment effect. If the drug were effective, there would be more patients in the placebo group needing rescue due to lack of efficacy, which was the case.

The sponsor argued that those who were transferred to the open-label arm were, not responding to treatment according to pre-specified rules and that the non-responder imputation was appropriate. The sponsor conducted alternative analyses including a multiple imputation analysis for week 52 remission (also submitted in the original application) and a logistic regression analysis for weeks 8 and 52 responders showing results consistent with the protocol-specified analysis. However, the strengths of these analyses are debatable. Observed case and complete case sensitivity analyses were also done, and these showed a numerical trend in favor adalimimab.

If it is reasonable to assume that subjects who terminated early would not have been in remission at week 52, had they stayed on assigned treatment, then the results may well be indicative a 9% treatment effect for adalimumab with regard to remission at week 52. It seems natural to assume that those who moved to open-label treatment failed to stay in remission, but it is not the case that all those in remission at week 52 had been so since week 8. The trial was not designed however to measure remission at weeks other than 8 and 52. Partial Mayo scores were collected at other weeks and used by the sponsor to support remission status over time.

The proportions of subjects who responded at both weeks 8 and 52 are more difficult to interpret since the effect size for that outcome was small (4%) in addition to the missing value concerns. Statistically, the effect at week 52 appears more convincing while treatment difference for both 8 and 52 responders is statistically marginal, but both results reached statistical significance per pre-planned analysis.

Reference ID: 3196046

Study 827 was not designed to demonstrate maintenance of remission, since subjects were not re-randomized after week 8; however the results at week 52 would seem to support a notion of durability or sustained remission under the condition that completers were in remission during the study, and that patients who terminated early were not in remission. The secondary endpoint of being in remission at both weeks 8 and 52 better supports the idea of a sustained remission but does not capture the time-course of remission throughout the study.

Overall conclusion

It seems clear that the studies met their primary statistical objectives for induction of clinical remission at week 8, and the sponsor's pre-specified statistical methods were applied appropriately. Study 827 demonstrated a statistically significant treatment effect for induction at 52 weeks and a small but significant effect for induction at both 8 and 52 weeks. However, statistical significance does not imply clinical significance, and whether or not the treatment differences observed in these studies are clinically meaningful was the key issue for the Advisory Committee.

The sponsor's complete response satisfactorily addressed many of the statistical issues raised in the CR letter. Although much of the resubmission was based on exploratory analyses, the results should be considered supportive.

Reference ID: 3196046

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/s/

MICHAEL E WELCH
09/27/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

SAFETY ASSESSMENT

BLA/Serial Number:	125057/232
Drug Name:	Humira (adalimumab)
Indication(s):	Treatment of ulcerative colitis
Applicant:	Abbott Laboratories
Date(s):	Consult received: 07/17/2012 PDUFA: 09/28/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 7
Statistical Reviewer:	Bradley McEvoy, DrPH, MS
Concurring Reviewers:	Team Leader: LaRee Tracy, PhD, MA
Medical Division:	Division of Gastroenterology and Inborn Error Products
Clinical Team:	Clinical Reviewer: Klaus Gottlieb, MD, MBA, MS Clinical Team Lead: Anil Rajpal, MD, MPH
Project Manager:	Kevin Bugin, MS

Keywords: Number Needed to Harm, Net Efficacy Adjusted for Risk, benefit-risk assessment

Backgound

This review is a summary and critique of the methods considered by the sponsor in their benefit-risk analysis. This review does not follow the standard statistical review template or format.

Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor alpha (TNF-α). Humira is FDA approved for treatment of adult patients with moderately and severely active rheumatoid arthritis, active psoriatic arthritis, active ankylosing spondylitis, and moderate to severely active polyarticular juvenile idiopathic arthritis. Supplemental BLA 125057/232 was submitted by the sponsor on January 25, 2011for a new indication for the treatment of adults with moderately to severely active ulcerative colitis (UC). On November 11, 2011 the Division of Gastroenterology and Inborn Errors Products (DGIEP) issued a complete response letter (CRL) stating the main approvability issues of concerns over selection of an appropriate dose and efficacy results that were sensitive to alternative analyses.

On July 17, 2012, DGIEP consulted the Division of Biometrics VII (DB7) to provide a statistical assessment of benefit-risk analyses provided by the sponsor in their March 30, 2012 formal response to the Agency's CRL and of the sponsor's briefing document for the August 28, 2012 Gastrointestinal Drugs Advisory Committee (GDAC) meeting. The quantitative benefit-risk analyses assessed by the statistical reviewer were the numbers need to treat (NNT) and the number needed to harm (NNH) analyses, a net-efficacy adjusted for risk (NEAR) analysis, and a serious adverse event (SAE) adjusted days in clinical remission analysis. This review summarizes the risk-benefit analyses provided by the sponsor along with comments on the statistical methods and limitations.

NNT and NNH Analyses

The sponsor's GDAC briefing document included NNT and NNH analyses that attempt to characterize the benefit and risk of the Humira intervention in relation to the randomized placebo group. *Note that this information was not included in the sponsor's formal response submission.* For both NNT and NNH, estimates were derived by taking the inverse of the risk difference (1/difference of proportions for outcome of interest between randomized treatment groups) based on pooled data from the two comparative UC trials or combined data from the UC and Crohn's disease trials (NNH only). NNT estimates were presented for clinical remission, clinical response, mucosal healing, and inflammatory bowel disease questionnaire (IBDQ) response. NNH estimates were presented for the incidence of any SAE, adverse events (AE) leading to study drug discontinuation, serious infection, and malignancy.

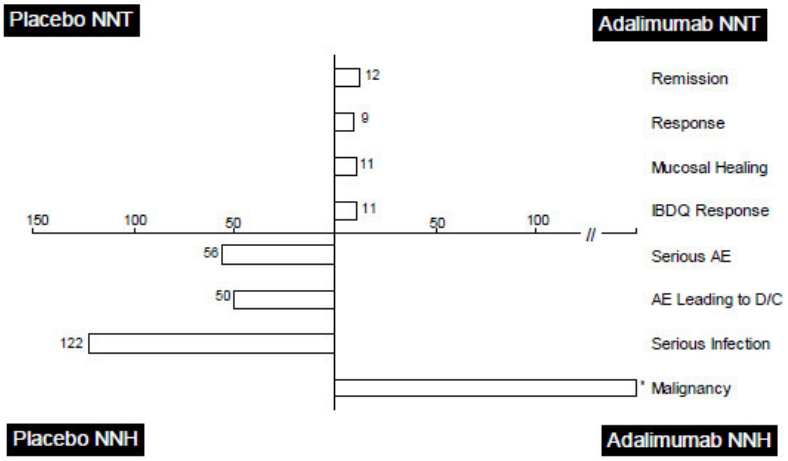
Statistical Limitations of the NNT and NNH Analyses

The main issue is that the sponsor's conclusion from the NNT and NNH analysis is not supported by the data. Specifically, the sponsor concludes (on page 111 of the briefing document), "In almost all cases, the risk of harm was greater with placebo, as reflected by positive NNH values for the placebo group. … The data demonstrate that the benefits outweigh the risks for adalimumab in UC" and provides Figure 1. This conclusion can not be supported by the data since confidence intervals (CI) around the NNT and NNH estimates all include the null value (±∞). Therefore, it is not possible to conclude with statistical certainty that the risks of harm were greater in the placebo group than in the Humira group. The CIs are illustrated in

Reference ID: 3200696

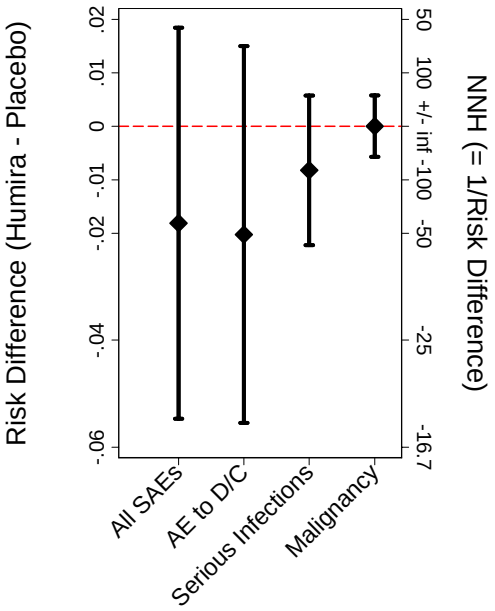
Figure 2, which was constructed by the statistical reviewer using the same data used by the sponsor to produce Figure 1.

Figure 1. NNT and NNH for weeks 0 to 52 (UC studies) from sponsor's GDAC briefing document



Source: Sponsor's GDAC background document: Figure 20, page 113

Figure 2. NNH and risk differences with 95% CIs for Week 0 to 52, Humira 160/80 vs. Placebo



Graph adapted from Altman[1]. Estimates based on pooled data from two comparative trials (M06-826 and M06-827) The diamonds represent the NNH or risk difference and the vertical bars are the confidence intervals around these estimates.

[1] Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998, (317) 1309-1312

Reference ID: 3200696

Other important shortcomings of the sponsor's analysis include pooling data from multiple trials and a lack of specificity when using composite safety endpoints. The issue of pooling data from multiple trials without properly adjusting, or accounting, for trial is it can yield confounded results since it does not preserve the within trial comparison established by randomization. The issue with considering a composite safety endpoint, where the component endpoints that define the composite may have differing levels of severity and timing of occurrence, is a loss of the specificity for the individual component endpoint.

NEAR Analyses

In an attempt to combine clinical efficacy and safety into a single composite estimate, the sponsor performed an analysis based on the NEAR approach described by Boada and colleagues[2,3]. The sponsor's NEAR analyses defined the composite benefit-risk endpoint as safety event-free treatment success, which included subjects with the efficacy response (e.g. clinical response) who also did not experience a particular safety event (e.g. serious infection). Results from the NEAR analyses are presented in both the response to the CRL and GDAC briefing document. The values of the composite endpoint, which were used to calculate the NEAR odds ratio (OR), were tabulated as follows:

Treatment Group	Responder w/o AE	Non-responders w/o AE	Responders with AE	Non-responders with AE
Humira	A1	B1	C1	D1
Placebo	A2	B2	C2	D2

The odds (responders without an AE/all other subjects in the same treatment group) of experiencing a safety event-free treatment success in the Humira 160/80 mg group were then compared to the odds in the placebo group with 95% confidence intervals calculated using standard methods. The NEAR OR was calculated as follows: (A1/(B1+C1+D1))/ (A2/(B2+C2+D2)). The sponsor interpreted a NEAR OR larger than one as a benefit-risk ratio in favor of Humira compared to placebo.

In the sponsor's GDAC briefing document, NEAR analyses were presented through week 8 using pooled data from trials 826 and 827 (Integrated analysis-set extended (IAS-E)), and through week 52 using the ITT analysis set from trial 827. At each time-point (week 8 or week 52), NEAR ORs were calculated for the efficacy endpoints of clinical response and clinical remission, and the safety events consisting of serious infection and any SAEs (which included serious infections). Results from the analyses are presented below. The estimated OR are all

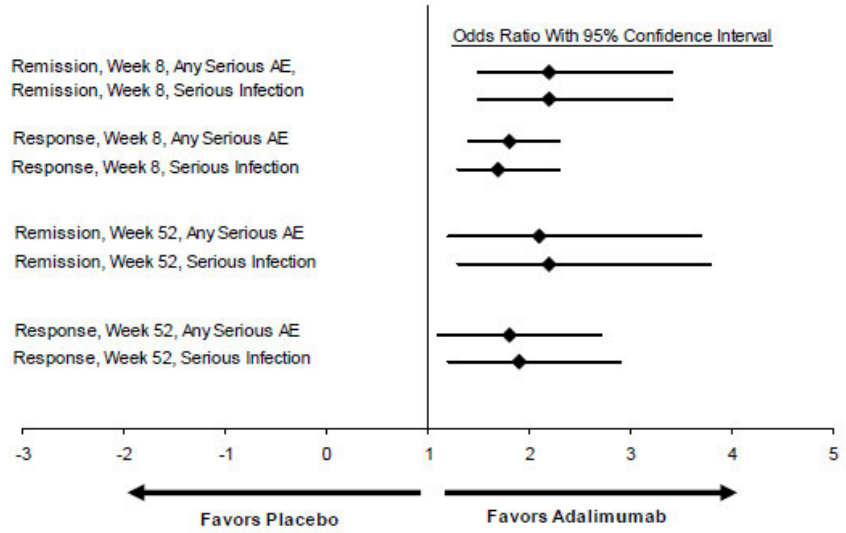
[2] Boada JN, Boada C, Garcia-Saiz M, et al. Net Efficacy Adjusted for Risk (NEAR): a simple procedure for measuring risk:benefit balance. PLoS One. 2008;3(10):e3570.

[3] The NEAR analysis performed by the sponsor differs from the approach described in the source publication. The NEAR methodology, as described in the publication, compares between treatment groups, the *expected* number of subjects that had a treatment success without experiencing a specific safety event. That is, rather than compare the *observed or actual* numbers of subjects that had a treatment success and not a safety event, the comparison is based on the *expected* count. The expected numbers are obtained by a questionable assumption that the efficacy and safety endpoint are independent. Use of the expected numbers is motivated by only having access to marginal events counts (e.g., published literature). Since the sponsor had patient-level data, the comparisons were based the observed number count rather than the expected under assumptions of independence.

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larger than 1 and the CIs all exclude 1, suggesting a statistically greater number of subjects in the Humira group that had a safety event-free treatment success compared to placebo. While these findings are favorable for Humira, they should be interpreted cautiously for reasons described in the following section "*Statistical Limitations with Sponsor's NEAR Analyses"*.

Figure 3. NEAR Analysis from sponsor's GDAC briefing document



Source: Sponsor's GDAC background document: Figure 22, page 116

Statistical Limitations with Sponsor's NEAR Analyses

Beyond issues previously raised regarding lumping or combining various safety endpoints into a single composite endpoint and pooling data from multiple trials without assigning weights, the ability of the sponsor's NEAR analysis to quantify benefit-risk in a clinically-meaningful way has the following limitations.

First, this approach implicitly assumes that the clinical benefit of having a clinical response is of equal importance or weight as experiencing a specific safety event. Such an assumption was not justified by the sponsor in any of the benefit-risk scenarios. Furthermore, it is potentially inappropriate to assume equal weights due to the varying degree of importance of both the safety and efficacy events. For example, a serious infection may be more or less important clinically than the occurrence of clinical response. The implication of this one-to-one exchange of efficacy for safety is illustrated by considering a hypothetical example. Consider the week 8 remission analysis for which 180/468 (38.5%) remissions were reported in the placebo group and 240/470 (51.1%) in the Humira group. Suppose there were 59 SAEs in the Humira group occurring in subjects that had a clinical response, and none in the placebo group. In this extreme hypothetical scenario showing an alarming safety signal disfavoring the Humira group, the NEAR OR is greater than 1, suggesting Humira has a favorable benefit-risk ratio. This example illustrates an obvious incongruence between the proposed quantification of benefit-risk to how clinical benefit is considered along with risk.

A second limitation of the sponsor's use of the NEAR method is that the comparisons only contrast the favorable aspects of benefit-risk, i.e. the numerator value is based on patients with

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clinical benefit who also did not experience the specific safety event of interest. Other important aspects of benefit-risk assessment, such as patients that *did not* have a clinical response (e.g. no remission) but *did* have a safety event, are not incorporated into the benefit-risk calculus.

A third limitation of the sponsor's use of the NEAR method is that the assessment of week 8 clinical outcome does not control for long-term safety. For example, the analyses used a week 8 assessment for efficacy but safety was not measured out to week 52. That is, assessing short-term efficacy with short-term safety provides an incomplete assessment of benefit-risk since short-term efficacy is balanced with both considerations for short-term safety and long-term safety. The failure of the analyses to account for timing of the event, in addition to the preceding two limitations, is sufficient reason to question the results from these analyses.

SAE-Adjusted Days in Remission

In the formal response to the CRL, the sponsor presented an exploratory analysis adjusting the days of clinical remission for days of serious adverse events (SAEs) leading to treatment discontinuation in trial 827; it is unclear from the report why this analysis was not performed using data from trial 826. *Note that this information was not included in the sponsor's GDAC background document.* In this analysis, the mean days of SAEs leading to treatment discontinuation was subtracted from days of clinical remission.

Despite the mean duration of SAEs being similar between the Humira 160/80 and placebo groups (4.11 and 4.64 days, respectively), the difference in SAE-adjusted days in clinical remission was statistically significantly different between groups. This difference is driven by the large difference in days of clinical remission (85.32 vs. 52.87 days in the Humira and placebo groups, respectively; p-value < 0.001). Therefore, it is unclear what additional information the SAE-adjusted analysis of days of clinical remission provides beyond what can be inferred from the analysis that only considered days of clinical remission. Furthermore, the clinical meaningfulness of this analysis is unclear given the pooling of all SAE time without accounting for type or severity of the event and the timing of the event in relation to clinical remission, if remission occurred.

Conclusion

Three quantitative benefit-risk analyses presented by the sponsor were found to have several important methodological limitations. These include an inability to account for unequal clinical relevance of safety and efficacy component endpoints in the composite measures, pooling events with differing severity or importance, failure to account for other benefit-risk scenarios, and failure to account for time-varying events. While these approaches attempt to present benefit-risk as a summary measure, they suffer from a loss of specificity and interpretability as used in this application. Therefore, these analyses and the sponsor's interpretation of the results from the analyses serve little, if any, useful function in the overall benefit-risk assessment for the use of Humira in patients with moderate to severe UC.

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/s/

BRADLEY W MCEVOY
10/09/2012

LAREE A TRACY
10/09/2012
I concur with this review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125057/232
Drug Name:	Humira (adalimumab)
Indication(s):	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
Applicant:	Abbott Laboratories
Date(s):	Received March 30, 2012 PDFUA: September 28, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Milton C. Fan, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Division Director	Steve Wilson, Dr. PH.
Medical Division:	Gastroenterology and Inborn Errors Drug Product (DGIEP)
Clinical Team:	Klaus Gottlieb, M.D., Anil Rajpal, M.D. (DGIEP)
Project Manager:	Kevin Bugin (DGIEP)

Keywords: clinical study, biological product, sensitivity analysis

Reference ID: 3192233

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor's resubmission included alternative analyses for remission rate at Week 8 for Study M06-826 and subgroup analyses for clinical remission at Week 8 for Study M06-826 and Study M06-827. These analyses provide some supportive evidence consistent with the treatment effects observed in the studies; however, the analyses were exploratory and do not alleviate the main review concerns raised in the CR letter.

The sponsor also provided an integrated analysis assessing the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy. This analysis should be considered hypothesis generating. Any potential treatment benefit would need to be confirmed in a prospectively designed study.

1.2 Statistical Issues and Finding

On January 25, 2011, the sponsor submitted a supplemental Biologics License Application (BLA) consisting of two adequate and well-controlled studies (M06-826 and M06-827) and an open-label safety study (M10-223) for the claim.

Study M06-826 , was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Study M06-827, was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Results from Studies M06-826 and M06-827 have been statistically reviewed. The original Statistical Review and Evaluation for this sBLA was documented on October 28, 2011.
A Complete Response Letter was issued for this sBLA on November 21, 2011. The statistical issues involved in CR Letter are listed below.

1. STUDY M06-826

a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP, 10.0 mg/L vs. CRP ~10.0 mg/L (13.4% vs. -4.5%).

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2. STUDYM06-827

a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1 % vs. 12.1 %.

c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

The sponsor’s resubmission presented re-analyses addressing statistical comments as included in the Complete Response Letter.

The sponsor also submitted the Hospitalization Report entitled, "Effects of Adalimumab Maintenance Therapy on the Risk of Hospitalization and Colectomy in Patients with Ulcerative Colitis: Results from an Analysis of 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies of the Human Anti-TNF Monoclonal Antibody Adalimumab for Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis (Study M06-826 and Study M06-827)."

The sponsor’s resubmission included alternative analyses for remission rate at Week 8 for Study M06-826 and for subgroup analyses for clinical remission at Week 8 for Study M06-826 and Study M06-827. These analyses should be considered exploratory.

For sponsor’s analysis of hospitalization and colectomy, the integrated analysis for assessing the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy in the pooled Study M06-826 and Study M06-827 trials was post-hoc and hypothesis generating.

Results from post-hoc or exploratory analyses intending to show treatment benefit should be confirmed in a prospectively designed study.

2. INTRODUCTION

2.1 Overview

On January 25, 2011, the sponsor submitted a supplemental Biologics License Application (BLA) consisting of two adequate and well-controlled studies (M06-826 and M06-827) and an open-label safety study (M10-223) to support the proposed indication.

Study M06-826, an induction trial, was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Study M06-827, an induction and maintenance trial, was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Results from Studies M06-826 and M06-827 were initially reviewed by this reviewer. The Statistical Review and Evaluation for this sBLA was documented on October 28, 2011. A complete response letter was issued on November 21, 2011.

This review addresses the March 30, 2012 complete response and also comments on the statistical issues raised at the GIDAC held on August 28, 2012.

These comments in this review are summarized from the primary review and are recommended as issues supplemental to the CR Letter. A main reason for the sensitivity of results for Study M06-826 was its smaller sample size. Both studies showed a small but similar treatment effect for induction. The remarks below on subgroup comparisons are exploratory but may be deemed clinically important.

Study M06-826

Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p=0.089). Moreover the significance of the analysis results is sensitive to the use of exact testing methods as well as the classification status based on a single subject.

Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent

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treatment effects were also shown in the subgroup analysis based on CRP < 10.0 mg/L vs. CRP ≥10.0 mg/L (13.4% vs. -4.5%).

Study M06-827

For Study M06-827, although the clinical remission rates, at weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both week 8 and week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

A subgroup analysis based on use of Azathioprine or 6-MP at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% vs. 12.1%.

A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at week 8 and at week 52) reflects a measure of durability as opposed to maintenance.

The statistical issues raised in CR Letter are listed below.

1. STUDY M06-826

   a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP, 10.0 mg/L vs. CRP ~10.0 mg/L (13.4% vs. -4.5%).

2. STUDYM06-827

   a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1 % vs. 12.1 %.

c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

The sponsor's resubmission included re-analyses addressing each of theses statistical comments as included in the Complete Response Letter.

The sponsor also submitted the Hospitalization Report entitled, "Effects of Adalimumab Maintenance Therapy on the Risk of Hospitalization and Colectomy in Patients with Ulcerative Colitis: Results from an Analysis of 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies of the Human Anti-TNF Monoclonal Antibody Adalimumab for Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis (Study M06-826 and Study M06-827)."

The Gastrointestinal Drugs Advisory Committee (GIDAC) of the Center for Drug Evaluation and Research met on August 28, 2012. The committee discussed the results from clinical trials of supplemental biologics license application (sBLA) 125057/232, for Humira (adalimumab for the proposed indication (use) for reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

2.2 Data Sources

The electronic submission was located at:
\\cber-fs3\m\eCTD Submissions\STN125057\125057.enx>

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Sponsor's Response to the CR Letter

3.1.1.1 Response to Clinical Comment 1

Clinical Comment 1 was:

Your submitted clinical trials are not deemed adequate to evaluate the efficacy of adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Our concerns are twofold.

First, although both trials demonstrated statistically significant improvement for adalimumab treatment relative to placebo, we note that statistical significance is lost in Study M06-826 if the responder status of 1 patient in the adalimumab 160/80/40 group is changed from responder to non-responder, or if the responder status of 1 placebo-treated patient is changed from non-responder to responder. Although the clinical remission rate at Week 8 in the adalimumab 160/80/40 treatment group for Study M06-826 was statistically higher than that in the placebo group (18.5% vs. 9.2%, p = 0.031), these results are sensitive to alternative analyses, and the conclusions are not considered robust from a statistical perspective. For example, adjusting the primary analysis for the significantly different baseline Mayo scores, the treatment differences were not significant (p = 0.085). Moreover the significance of the analysis results is sensitive to the use of exact testing methods.

The sponsor's responses to Clinical Comments 1 were:

To address the Clinical Comment 1, the sponsor provided supplemental analyses that: 1) examine the totality of efficacy data from Study M06-826; 2) examine the totality of the efficacy data from the integrated analyses of data from Study M06-826 and Study M06-827; and 3) demonstrate the clinical relevance and robustness of the efficacy data.

The supplemental analyses and additional data in response to Clinical Comment 1 include:

- Intent-to-treat (ITT) analyses for the primary and secondary efficacy endpoints pre-specified in the final Statistical Analysis Plan (SAP) for Study M06-826 that included all subjects enrolled in Study M06-826 regardless of which protocol amendment the subjects were enrolled under (i.e., ITT-Extended [ITT-E] Analysis Set).

- Integrated analyses for the primary and secondary efficacy endpoints pre-specified in the final integrated SAP prior to the unblinding of Study M06-826 and Study M06-827 using the Integrated Analysis Set-Extended (IAS-E) Analysis Set.

There are three primary efficacy analysis sets used in this response:

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1. The ITT-E Analysis Set for Study M06-826, as defined in the CSR (R&D/09/143) included all subjects with confirmed UC at Baseline who were randomized according to the original protocol or any of the 4 protocol amendments and received at least 1 injection of the following induction regimens: adalimumab 160/80/40 mg eow, adalimumab 80/40 mg eow, or placebo.

2. The ITT Analysis Set for Study M06-827, as defined in the CSR (R&D/10/236) included subjects with confirmed UC at Baseline who were randomized, and excluded subjects from Sites 22635, 36809, and 27010. These sites were noncompliant with Good Clinical Practice (GCP) and protocol requirements.

3. The IAS-E Analysis Set (Induction and Maintenance Analysis Set – Study M06-827 and Study M06-826), as defined in the Integrated Summary of Efficacy (ISE) (R&D/10/239), was used for efficacy analyses at Week 8 and Week 8 through Week 52. The IAS-E Analysis Set included all randomized subjects with confirmed UC who received at least 1 dose of blinded study drug in either Study M06-826 or Study M06-827 (excluding Sites 22635, 36809, 27010 for noncompliance). This included all subjects in the ITT-E Analysis Set from Study M06-826.

The FDA's comments included the clinical remission rate for the pre-specified primary endpoint of Study M06-826 at Week 8 in the adalimumab 160/80/40 mg group, which was statistically significantly higher compared with the placebo group (18.5% versus 9.2%, p = 0.031). With regard to alternative statistical analyses, the primary endpoint from Study M06-826 (ITT-A3) was reanalyzed using Fisher's exact test and statistical significance remained (p = 0.047).

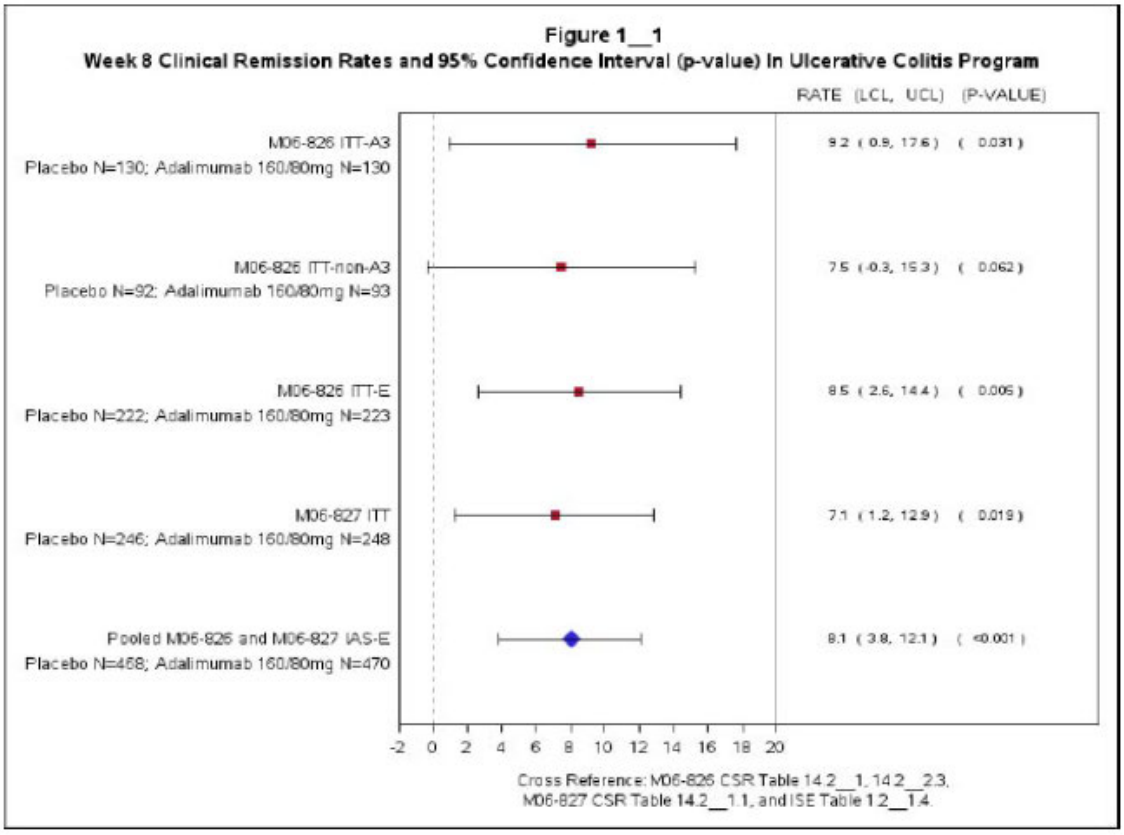
When adjusting the primary analysis for the Baseline Mayo scores, the sponsor was able to replicate the FDA's post-hoc covariate analysis with Baseline Mayo score as a stratification factor. However, this Cochran-Mantel-Haenszel (CMH)-based analysis included low subject counts for the Baseline Mayo scores of 6, 11, and 12.

The sponsor performed three alternative analyses based on the CMH test, using Baseline Mayo score as a stratification factor by categorizing Baseline Mayo score by median, tertiles, and quartiles, where Baseline Mayo scores with low subject counts were combined. All 3 analyses using the ITT-A3 subjects resulted in p values < 0.05 for treatment differences (See Appendix Tables 1-3).

The estimated treatment difference for achieving clinical remission per full Mayo (FM) score at Week 8 between adalimumab and placebo using the ITT-A3 Analysis Set from Study M06-826 was consistent with results using the ITT Analysis Set from Study M06-827 and the IAS-E Analysis Set from Study M06-826 and Study M06-827 as shown in the Figure below. In addition, within Study M06-826, the estimated treatment difference between adalimumab and placebo was consistent when using the ITT-E Analysis Set and the ITT-non A3 Analysis Set.

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Treatment Difference in Week 8 Clinical Remission Rates Between Adalimumab 160/80/40 mg and Placebo Including 95% CIs (*P* value) in the UC Clinical Development Program



3.1.1.2 Response to Statistical Comments 1a

Statistical comment1a was:

Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP, 10.0 mg/L versus CRP ~10.0 mg/L (13.4% vs. –4.5%).

The sponsor's responses to Statistical Comment 1a were as follows:

The sponsor stated that the skew observed in CRP subgroup analyses for Study M06-826 can be explained by the imbalance in the proportions of subjects across the Baseline CRP categories (defined as < 10 mg/L and ≥ 10 mg/L).

The sponsor performed the subgroup analysis analyses for clinical remission at Week 8 using the integrated data (DB data from Study M06-826 and Study M06-827, IAS-E Analysis Set).

The results for subgroups of CRP Corticosteroid use, Azathioprine/6-mercaptopurine use, aminosalcylate use, prior anti-TNF use, and presence of pancolitis are given below.

Number and Percentage of Subjects in Clinical Remission per Mayo Score at Week 8 by Subgroup (IAS-E Analysis Set; NRI)

	Placebo		ADA 160/80/40		
Subgroup	**N[a]**	**n (%)**	**N[a]**	**n (%)**	**95% CI[b]**
CRP (high sensitivity)[c] (mg/L)					
< 10	331	29 (8.8)	337	65 (19.3)	(5.3, 15.8)
≥ 10	130	7 (5.4)	127	9 (7.1)	(–4.5, 7.4)
Corticosteroid use[c]					
Yes	278	24 (8.6)	282	47 (16.7)	(1.9, 13.0)
No	190	13 (6.8)	188	28 (14.9)	(2.5, 15.2)
Azathioprine/6-mercaptopurine use[c]					
Yes	165	16 (9.7)	177	24 (13.6)	(–3.2, 10.4)
No	303	21 (6.9)	293	51 (17.4)	(5.2, 15.7)
Aminosalicylate use[c]					
Yes	320	24 (7.5)	326	55 (16.9)	(4.3, 14.4)
No	148	13 (8.8)	144	20 (13.9)	(–2.8, 11.9)
Prior anti-TNF use					
Yes	101	6 (5.9)	97	9 (9.3)	(–4.1, 10.7)
No	145	15 (10.3)	150	31 (20.7)	(2.0, 18.6)
Presence of pancolitis[c]					
Yes	252	21 (8.3)	234	40 (17.1)	(2.8, 14.6)
No	216	16 (7.4)	236	35 (14.8)	(1.6, 13.2)

As seen from Table above, at Week 8, all subgroup analyses showed positive treatment effects in favor of adalimumab was achieved for the majority of the subgroups. Particularly, the positive treatment effects in favor of adalimumab were observed for the Baseline CRP subgroup categories.

The sponsor also performed subgroup analyses for clinical remission at Week 52 for Study M06-828. The median CRP value was used as the cut-off for the subgroup analysis as this allowed for an equal distribution across Baseline CRP categories. Results for subgroup analysis for clinical remission at Week 52 for CRP at baseline are given below.

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Number and Percentage of Subjects in Clinical Remission per Mayo Score at Week 52 by Median of Baseline CRP (Study M06-827 ITT Analysis Set; NRI)

	Placebo (N = 246)		ADA 160/80/40 (N = 248)		
Baseline CRP	N	n (%)	N	n (%)	95% CI[a]
< Median = 4.13 mg/L	122	13 (10.7)	124	27 (21.8)	(2.0, 20.2)
≥ Median = 4.13 mg/L	124	8 (6.5)	123	16 (13.0)	(-0.8, 13.9)

a. Based on normal approximation.

Note: The median of Baseline CRP of all Study M06-827 ITT (placebo and adalimumab) subjects.

Cross reference: Table 2__1.8

3.1.1.3 Response to Statistical Comments 2a

Statistical Comment 2a was:

For Study M06-827, although the clinical remission rates at Week 8 and Week 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, *P* = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fisher's exact test, *P* = 0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

The sponsor's responses to Statistical Comment 2a were:

Regarding the first part of the FDA's comment referring to Fisher's exact test, it is more appropriate to use CMH test because Study M06-827 was randomized using prior anti-TNF use as a stratification factor. The choice of anti-TNF use as a pre-specified stratification factor was based on an expected difference in clinical response due to prior anti-TNF use.

To address the statistical robustness in Study M06-827, the first ranked secondary endpoint of sustained clinical remission at Weeks 8 and 52 was analyzed by the sponsor using the alternative methodology of logistic regression with treatment group as the factor. Based on this analysis, the statistical significance remained (*P* = 0.048).

Regarding the second part of the FDA's comment referring to early drop-outs, the design of Study M06-827 permitted subjects who had an inadequate clinical response to

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DB treatment to move to OL adalimumab starting at Week 12 of the study rather than discontinuing from the study outright. These rules for escape were as follows:

- Partial Mayo (PM) score ≥ Baseline score on 2 consecutive visits at least 14 days apart (for subjects with a PM score of 4 to 7 at Baseline).
- PM score ≥ 7 on 2 consecutive visits at least 14 days apart (for subjects with a PM score of 8 or 9 at Baseline).

The above criteria allowed escape for all subjects, even for subjects who were showing some improvement. These allowances were necessary to allow for adequate upfront study enrollment and were required to satisfy the needs of ethics committees, subjects, and investigator physicians.

Summary of number and percentage of subjects who discontinued the study during the DB period or Moved to OL Adalimumab for Study M060-827 is given below.

Number and Percentage of Subjects who Discontinued the Study During the DB Period or Moved to OL Adalimumab (Study M06-827, ITT Analysis Set)

	Placebo N = 246		ADA 160/80/40 N = 248	
Subject Status	n (%)	E/PY (PY = 114.3)	n (%)	E/PY (PY = 139.9)
Discontinued study during DB period	55 (22.4)	0.48	50 (20.2)	0.36
Due to AE of worsening of UC or lack of efficacy[a]	34 (13.8)	0.30	36 (14.5)	0.26
Due to reason other than AE of worsening of UC or lack of efficacy[b]	21 (8.5)	0.18	14 (5.6)	0.10
AE	11 (4.5)	0.10	3 (1.2)	0.02
Withdrew Consent	1 (0.4)	0.01	3 (1.2)	0.02
Lost to follow-up	0	0	1 (0.4)	0.01
Protocol violation	3 (1.2)	0.03	1 (0.4)	0.01
Other	6 (2.4)	0.05	6 (2.4)	0.04
Moved to OL	135 (54.9)	1.18	116 (46.8)	0.83
Discontinued study during DB period due to lack of efficacy, worsening of UC, or moved to OL therapy[c]	169 (68.7)	1.48	152 (61.3)	1.09
Completed DB period	56 (22.8)	0.49	82 (33.1)	0.59

a. Based on all reasons for discontinuation during DB period.

b. Based on primary reason for discontinuation during DB period.

c. Row 1 + Row 9 = Row 10.

Cross reference: Table 2__6.16, Table 4__2, Table 4__3.1

As seen from Table above, the higher placebo drop-out rate was due to OL escape for inadequate response and lack of efficacy; therefore, the NRI method applied to the

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primary endpoint is appropriate in these cases. Thus, this elevated rate would not undermine overall conclusions which support the superiority of adalimumab over placebo.

The sponsor performed the multiple imputation (MI) method for primary efficacy endpoint at Week 8. Results from multiple imputation (MI) are given below.

Multiple Imputation Analysis of Primary Efficacy Endpoint at Week 8 (Study M06-826, ITT-A3 Analysis Set; Study M06-827 ITT Analysis Set)

	Placebo %[a]	ADA 160/80/40 %[a]	*P* value
Study M06-826			
Primary Endpoint: Clinical remission at Week 8	9.5	19.1	0.028[b]
Study M06-827			
Co-Primary Endpoint 1: Clinical remission at Week 8	9.7	17.3	0.017[c]
Co-Primary Endpoint 2: Clinical remission at Week 52	25.5	37.0	0.034[c]

a. Only subjects with nonmissing values were included in the MI analyses.

b. *P* value to compare active treatment with placebo based on chi-square test (or Fisher's exact test if ≥ 20% of cell had expected cell count < 5).

c. *P* value to compare adalimumab with placebo based on Cochran-Mantel-Haenszel (CMH) test (stratification levels: prior anti-TNF versus anti-TNF-naïve).

Cross reference: agency-response-2011-may-09 Table 1, Table 2

3.1.1.4 Response to Statistical Comments 2b

Statistical Comment 2b was:

A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; –2.1% vs. 12.1%.

The sponsor's response to Statistical Comment 2b was:

At Week 8, all 14 subgroup analyses showed positive treatment effects and statistical significance in favor of adalimumab was achieved for the majority of the subgroups for integrated data which includes all Study M06-826 and Study M06-827 IAS-E DB data from.

3.1.1.5 Response to Statistical Comments 2c

Statistical Comments 2c was:

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A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The Sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

The sponsor's responses to Statistical Comments 2c were:

The sponsor understands the FDA's additional comments in the Complete Response Letter, and, therefore, proposes the following revised indication in this resubmission.

> HUMIRA is indicated for reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

It should be noted that the adalimumab parallel group design is similar to the infliximab Phase 3 study design where remitters or responders were not re-randomized.

3.1.2 Effects of Adalimumab Maintenance Therapy on the Risk of Hospitalization and Colectomy in Patients with Ulcerative Colitis: Results from an Analysis of 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies of the Human Anti-TNF Monoclonal Antibody Adalimumab for Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis (Study M06-826 and Study M06-827)

3.1.2.1 Background

The incidence in North America is estimated at 2.2 to 14.3 cases per 100,000 person-years with a prevalence of 37 to 246 cases per 100,000 persons.1 The burden of UC on the health care system is profound, accounting for nearly 500,000 physician visits and more than 47,000 hospitalizations per year in the United States (US) alone. The cost of ulcerative colitis (UC) in the United States in 2008 was estimated to be $8.1 to $14.9 billion, of which a significant portion is direct medical costs related to hospitalizations and surgeries.

The objectives of this integrated analysis were to assess the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy in the pooled Study M06-826 and Study M06-827 trials. Hospitalization is an important outcome for patients with any disease. A patient in hospital is a patient with impaired work productivity and poor quality of life. It can be considered a hard endpoint for assessing benefits of a therapy. Reduction of hospitalization would reflect a therapy's tangible benefits to patients, which is relevant to patients, physicians, and society. In addition, hospitalization, especially all-cause hospitalization can be viewed as composite indicator for benefit-risk profile of a therapy since it includes hospitalization due to adverse events of the therapy, collected

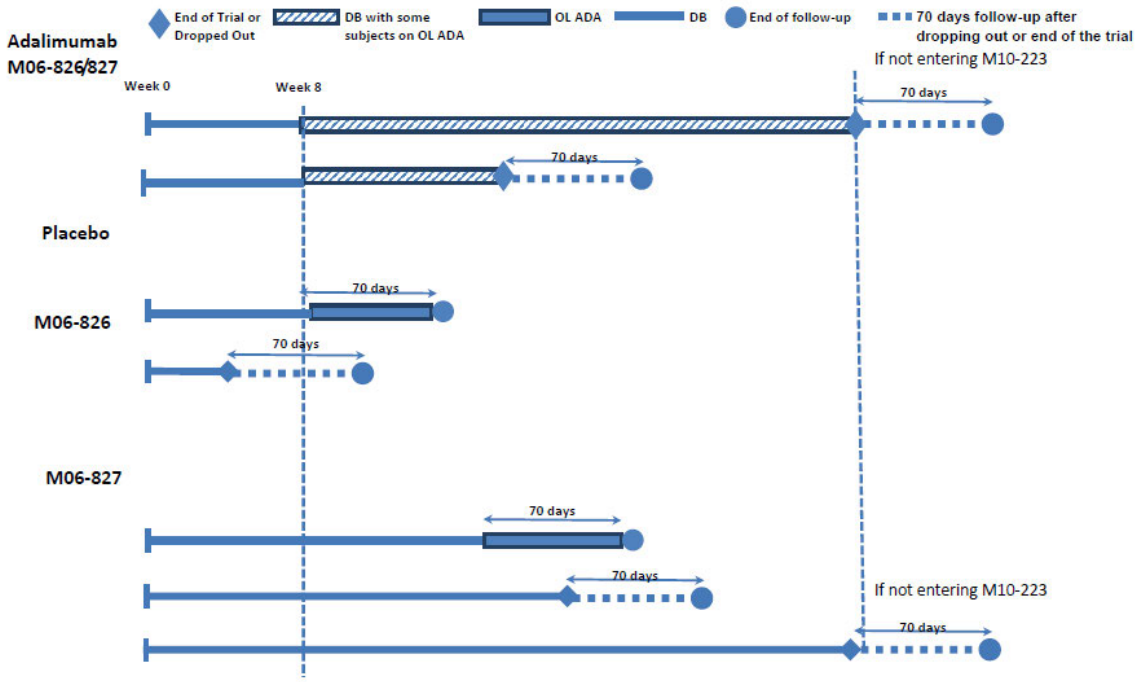
prospectively, and every hospitalization is considered a serious adverse event in clinical trials.

3.1.2.2 Sponsor's Results

In the analysis, there are two comparison groups: pooled placebo from Study M06-826 and Study M06-827, pooled adalimumab from Study M06-826 and Study M06-827. For Study M06-826, the adalimumab 160/80 mg and placebo treatment groups of the ITT-E population were included. For Study M06-827, all patients in the ITT population were included.

As described in Figure below, patients could have different follow-up periods:

Hospitalization Events Follow-up



- For adalimumab-treated patients in both studies, the follow-up period comprised the DB period plus the OL period if the patient entered the OL period (including adalimumab 40 mg eow and ew therapy).
    - For patients who withdrew from the study, the follow-up period was 70 days after the last dosing date. (e.g., the second line in Figure). The 70-day duration for the follow-up period was chosen because it represents 5 times the half-life of adalimumab. In addition, 70 days after the last dose of adalimumab is the standard follow-up time in the adalimumab ulcerative colitis and Crohn's disease clinical program.

- For those who completed the trials, the follow-up period was the last study date of Study M06-826 and Study M06-827 if they entered the UC open label extensions trial (Study M10-223).

- For those who completed the trials and did not enter Study M10-223, the follow-up period was 70 days after the last dosing date of Study M06-826 and Study M06-827 (e.g., the first line in Figure).

- For placebo-treated patients, the follow-up period was generally the DB period plus the 70-day follow-up (e.g., the fourth line in Figure) or the last study day of Study M06-826 and Study M06-827 if they rolled over into the extension trial (Study M10-223).

    - If a patient withdrew from the study during the DB period, the follow-up was 70 days after the last dosing date (e.g., the fourth and sixth lines in Figure).

    - For placebo-treated patients who switched to OL adalimumab the follow-up period depended on whether they enrolled into the follow-on Study M10-223 trial. For those placebo-treated patients who did not enroll in Study M10-223, the follow-up period was 70 days after the date they switched to OL treatment (e.g., the fifth line in Figure). For placebo-treated patients who did enroll in Study M10-223, the end of the follow-up period was the earlier date of either 70 days after switching to OL adalimumab or the last study date in Study M06-826 or Study M06-827 prior to enrollment in Study M10- 223.

For patients who switched from placebo to OL adalimumab, hospitalizations/colectomies that occurred during the first 70 days of OL adalimumab were attributed to placebo to capture the potential for delayed hospitalization/colectomy resulting from the failure of placebo therapy in the DB period.

The outcomes examined in this analysis were all-cause hospitalizations, UC-related hospitalizations, UC- or drug-related hospitalizations, and colectomy.

Events of hospitalization and colectomy were identified by a review of serious adverse events (SAEs) or AEs leading to discontinuation narratives from the study reports and Council for International Organizations of Medical Sciences (CIOMS) expedited reports.

Two external gastroenterologists who were blinded to the treatment assignment performed the review. Any disagreement at the initial assessment between two reviewers was resolved through further review by the same reviewers. Hospitalization was categorized into the following groups:

- All-cause hospitalizations: Defined as SAEs resulting in admission to the hospital for any reason.

- UC-related hospitalizations: Defined as hospital admissions due to adverse events (AEs) or complications that were related to UC and included the following categories: UC-related surgery; hospitalizations for nonsurgical

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UC-related events, such as UC-related flares; and hospitalizations related to the complications/extraintestinal manifestations of UC.

- Drug-related hospitalizations: Defined as hospital admissions due to potential adverse events related to medications used to treat UC (e.g., anti-TNF, steroids and/or immunomodulators). The identification of drug-related hospitalization was based on the judgment of the external gastroenterologists.

Analyses were performed for the following population data sets:

- All patients – adalimumab versus placebo
- Week 8 adalimumab (W8 ADA) responders per full Mayo score versus all placebo
- Week 8 ADA responders per partial Mayo score versus all placebo
- Week 8 adalimumab (W8 ADA) responders versus Week 8 adalimumab nonresponders per full Mayo score
- Week 8 adalimumab (W8 ADA) responders versus Week 8 adalimumab nonresponders per partial Mayo score

Clinical response per full Mayo score was defined as a decrease in Mayo score of ≥ 3 points from Baseline and a decrease in Mayo score of ≥ 30% from Baseline and decrease in the rectal bleeding score (RBS) ≥ 1 or an absolute RBS of 0 or 1.

Partial Mayo score response is defined as a decrease from Baseline in partial Mayo score ≥ 2 points AND a decrease from Baseline in partial Mayo score ≥ 30% and decrease in the rectal bleeding score (RBS) ≥ 1 or an absolute RBS of 0 or 1.

The total patient population comprised 939 patients with 471 and 468 patients in the adalimumab 160/80 mg and placebo treatment arms, respectively. The W8 ADA responders based on full Mayo score comprised 241 patients. If partial Mayo score was used, the W8 ADA responder population comprised 242.

Note that the *P* value for comparisons of adalimumab Week 8 responders versus nonresponders should be considered non-inferential. The corresponding nonresponder data is also provided as a reference.

Incidence rates for hospitalizations (all-cause, UC-related, and UC- or drug-related) and colectomy were calculated as the number of patients with the respective event divided by the time at risk. For patients with an event during the study period, time at risk was the patient-years (PYs) from baseline to the first event. For patients without an event during the study period, time at risk was PYs from baseline to the end of study follow-up period. The event date was defined as the date of admission to the hospital for hospitalization and the admission date of colectomy or the earliest of the surgery referral date for a subsequent colectomy. Relative risk ratios and confidence intervals were calculated to evaluate the statistical significance of the difference between the 2 arms.

The numbers of all-cause and UC-related hospitalizations as well as the combined

category of UC- or drug-related hospitalizations during the study period were compared for adalimumab 160/80 mg and 40 mg eow/ew thereafter versus placebo using Poisson regression, with the length of follow-up as the offset variable.[4] Poisson regression has been used to analyze counts of events in previous studies for similar analyses. Multiple events were allowed to be counted in this model.

3.1.2.2.1 All Cause or UC-Related Hospitalization

the overall follow-up time in the all patient population was longer for adalimumab-treated patients than placebo-treated patients (e.g., for UC-related hospitalization the time was 389 PYs for adalimumab and 216 PYs.
for placebo.

The proportions of patients with all-cause and UC-related hospitalization events by treatment group are presented below.

Analysis of All-Cause and UC-Related Hospitalizations in Study M06-826 and Study M06-827

Outcome	n/PYs at Risk[a] (%) Adalimumab 160/80[c]	Placebo	Relative Risk of Adalimumab/Placebo (95% CI)	*P* value[b]
All patients population: 160/80 ADA vs. all placebo	**N = 471**	**N = 468**		
All-cause hospitalization	67/379 (18)	56/214 (26)	0.7 (0.5, 1.0)	0.030
UC-related hospitalization	45/389 (12)	47/216 (22)	0.5 (0.4, 0.8)	0.002
W8 ADA 160/80 responder (full Mayo score) population vs. all placebo	**N = 241**	**N = 468**		
All-cause hospitalization	25/219 (11)	56/214 (26)	0.4 (0.3, 0.7)	0.0004
UC-related hospitalization	12/225 (5)	47/216 (22)	0.2 (0.1, 0.4)	< 0.0001
W8 ADA 160/80 responder (partial Mayo score) population vs. all placebo	**N = 242**	**N = 468**		
All-cause hospitalization	25/219 (11)	56/214 (26)	0.4 (0.3, 0.7)	0.0004
UC-related hospitalization	14/224 (6)	47/216 (22)	0.3 (0.2, 0.5)	< 0.0001

ADA = adalimumab; CI = confidence interval

a. Reflected as denominators in the columns.

b. *P* values based on Z score approximation.

c. Including 40 mg eow and ew.

As seen from Table above, for all-cause hospitalization, the incidence rates for UC-related hospitalization were lower in the adalimumab group than in the placebo group (18% versus 26%, respectively). For UC-related hospitalization, the rates were 12% in the adalimumab group and 22% in the placebo group. For the W8 ADA responder population based on full Mayo score, the

incidence rates for UC-related hospitalization were also lower in the adalimumab group than in the placebo group (5% versus 22%, respectively). Similar results were obtained if the W8 ADA responder population was based on partial Mayo score.

The number of hospitalizations by treatment arm is presented in Table below. The total number of hospitalizations was counted as an alternative to counting number of patients with at least 1 hospitalization as in Table below.

Poisson Regression Analysis of All-Cause and UC-Related Hospitalizations in Study M06-826 and Study M06-827

Outcome	E/100 PYs at Risk[a] (%)		*P* value[b]
	Adalimumab 160/80[c]	Placebo	
All patients population: 160/80 ADA vs. all placebo	**N = 471**	**N = 468**	
All-cause hospitalization	83/401 (21)	69/224 (31)	0.0151
UC-related hospitalization	54/401 (13)	57/224 (25)	0.0008
W8 ADA 160/80 responder (full Mayo score) population vs. all placebo	**N = 241**	**N = 468**	
All-cause hospitalization	33/229 (14)	69/224 (31)	0.0004
UC-related hospitalization	14/229 (6)	57/224 (25)	< 0.0001
W8 ADA 160/80 responder (partial Mayo score) population vs. all placebo	**N = 242**	**N = 468**	
All-cause hospitalization	33/229 (14)	69/224 (31)	0.0003
UC-related hospitalization	16/229 (7)	57/224 (25)	< 0.0001

ADA = adalimumab

a. Reflected as denominators in the columns.

b. *P* values based on Z score approximation.

c. Including 40 mg eow and ew.

As seen from Table above, in the all patient population, the event rate of all-cause hospitalizations was lower in the adalimumab maintenance group compared with the placebo group (21 versus 31 hospitalizations per 100 PYs). The event rate of UC-related hospitalizations was also lower in the adalimumab maintenance group compared with the placebo group (13 versus 25 hospitalizations per 100 PYs).

In the W8 ADA responder population based on full Mayo score, the event rate of all-cause (14 versus 31 hospitalizations per 100 PYs) and UC-related hospitalizations (6 versus 25 hospitalizations per 100 PYs) was also lower in the adalimumab group. Similar results were obtained when the W8 ADA responder population was based on partial Mayo score.

3.1.2.2.2 UC or Drug Related Hospitalization

The proportions of patients with UC- or drug-related hospitalizations by treatment arm are provided in Table below.

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Analysis of UC- or Drug-Related Hospitalizations in Study M06-826 and Study M06-827

Outcome	n/PYs at Risk[a] (%)		Relative Risk of Adalimumab/Placebo (95% CI)	*P* value[b]
	Adalimumab 160/80[c]	Placebo		
All patients population: 160/80 ADA vs. all placebo	**N = 471**	**N = 468**		
UC- or drug-related hospitalization	53/385 (14)	51/215 (24)	0.6 (0.4, 0.8)	0.005
W8 ADA 160/80 responder (full Mayo score) population vs. all placebo	**N = 241**	**N = 468**		
UC- or drug-related hospitalization	14/225 (6)	51/215 (24)	0.3 (0.2, 0.5)	< 0.0001
W8 ADA 160/80 responder (partial Mayo score) population vs. all placebo	**N = 242**	**N = 468**		
UC- or drug-related hospitalization	16/224 (7)	51/215 (24)	0.3 (0.2, 0.5)	< 0.0001

ADA = adalimumab; CI = confidence interval

a. Reflected as denominators in the columns.

b. *P* values based on Z score approximation.

c. Including 40 mg eow and ew.

As seen from Table above, in the all patient population, significantly fewer patients in the adalimumab group were hospitalized for UC- or drug-related events versus placebo (14% and 24%, respectively). For the W8 ADA responder population based on full Mayo score, the incidence rate was also lower in the adalimumab group than in the placebo group (6% versus 24%). Similar results were obtained when the W8 ADA responder population was based on partial Mayo score.

The sponsor also performed Poisson regression analysis of UC- or drug-related hospitalizations in Study M06-826 and Study M06-827. The results are given below.

Poisson Regression Analysis of UC- or Drug-Related Hospitalizations in Study M06-826 and Study M06-827

Outcome	E/100 PYs at Risk[a] (%)		*P* value[b]
	Adalimumab 160/80[c]	Placebo	
All patients population: 160/80 ADA vs. all placebo	**N = 471**	**N = 468**	
UC- or drug-related hospitalization	63/401 (16)	61/224 (27)	0.0023
W8 ADA 160/80 responder (full Mayo score) population vs. all placebo	**N = 241**	**N = 468**	
UC- or drug-related hospitalization	16/229 (7)	61/224 (27)	< 0.0001
W8 ADA 160/80 responder (partial Mayo score) population vs. all placebo	**N = 242**	**N = 468**	
UC- or drug-related hospitalization	18/229 (8)	61/224 (27)	< 0.0001

ADA = adalimumab

a. Reflected as denominators in the columns.

b. *P* values based on Poisson regression with time offset.

c. Including 40 mg eow and ew.

As seen from Table above, in the all patient population, the number of UC- or drug-related hospitalizations in the adalimumab and placebo groups was 16 versus 27 hospitalizations per 100 PYs. Similarly, the event rate of UC- or drug-related hospitalizations in the adalimumab group was also lower than placebo (7 versus
27 hospitalizations per 100 PYs) in the W8 ADA responder population based on full Mayo score. Similar results were obtained when the W8 ADA responder population was based on partial Mayo score.

3.1.2.2.3 Colectomy

The sponsor performed analysis of colectomy in Study M06-826 and M06-827. Results are given below.

Analysis of Colectomy in Study M06-826 and Study M06-827

Outcome	n/PYs at Risk[a] (%) Adalimumab 160/80[c]	Placebo	Relative Risk of Adalimumab/Placebo (95% CI)	*P* value[b]
All patients population: ADA 160/80 vs. all placebo	**N = 471**	**N = 468**		
Colectomy	14/399 (3.5)	10/224 (4.5)	0.8 (0.3, 1.8)	0.56
W8 ADA 160/80 responder (full Mayo score) population vs. all placebo	**N = 241**	**N = 468**		
Colectomy	1/229 (0.4)	10/224 (4.5)	0.1 (0, 0.5)	0.0060
W8 ADA 160/80 responder (partial Mayo score) population vs. all placebo	**N = 242**	**N = 468**		
Colectomy	1/229 (0.4)	10/224 (4.5)	0.1 (0, 0.5)	0.0059

ADA = adalimumab; CI = confidence interval

a. Reflected as denominators in the columns.

b. *P* values based on Z score approximation.

c. Including 40 mg eow and ew.

As seen from Table above, in the all patient population, the incidence rates per 100 PYs of colectomy in the adalimumab and placebo groups were 3.5% and 4.5%, respectively. In the W8 ADA responder population based on full Mayo score, the incidence rate per 100 PYs of colectomy was lower in the adalimumab group compared with the placebo group (0.4% versus 4.5%, respectively). Similar results were obtained when the W8 ADA responder population was based on partial Mayo score.

3.1.3 Reviewer's Comments

3.1.3.1 Clinical Comment 1

Low subject counts for the Baseline Mayo scores of 6, 11, and 12 were observed. But, these counts exceeded minimum of 5. So, the Cochran-Mantel-Haenszel (CMH) test was a valid test for adjusting baseline Mayo score.

The sponsor performed three alternative analyses based on the CMH test, using Baseline Mayo score as a stratification factor, were performed by categorizing baseline Mayo score by median, tertiles, and quartiles. The categorizing baseline Mayo score was not pre-specified and should be considered as hypotheses generating.

However, it was found that there were statistically significant differences across treatment groups for Mayo score at baseline in the ITT-A3 Set (chi-square p-value 0.0044) as seen below.

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Mayo Score at Baseline
Study M06-826
(ITT-A3 Set)

Frequency Row Pct	6	7	8	9	10	11	12	Total
ADALIMUMAB 160/80/40 MG EOW	15 11.54	13 10.00	24 18.46	33 25.38	25 19.23	15 11.54	5 3.85	130
ADALIMUMAB 80/40 MG EOW	9 6.92	10 7.69	36 27.69	26 20.00	22 16.92	17 13.08	10 7.69	130
PLACEBO	9 6.92	28 21.54	19 14.62	27 20.77	34 26.15	8 6.15	5 3.85	130
Total	33	51	79	86	81	40	20	390

For the proportion of subjects with remission at Week 8, the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score (p=0.0852).

The sponsor stated in the Response to Information Request dated May 09, 2011 that due to windowing rules for dosing (±3 days), one subject in Adalimumab 160/80/40 had a response attributed to Week 8 in the Observed Case analysis but did not receive the Week 8 dose of adalimumab (i.e., was not a completer). This subject was considered as a responder in the sponsor's analysis of primary efficacy endpoint: proportion of subjects with remission at We

In the Response to Information Request dated September 09, 2001, it was stated that three subjects (1 subject in each treatment group) from Study M06-826 were included in the OC (observed case) analysis but not the CC (complete case) analysis for remission at Week 8 because although they had Week 8 evaluations, they did not receive the Week 8 dose of adalimumab and were therefore not considered completers. The subject in adalimumab 160/80/40 treatment group is as follows:

- Subject 63951 (adalimumab 160 80/40 treatment group) was a 29-year-old male with a Baseline Mayo score of 6 who received study drug at Week 0 only and was discontinued due to a protocol violation. The subject entered the study with a Mayo score of 6 and after discontinuation the partial Mayo score at Day 54 was reported to be 0.

So, the remission status of this subject (responder or non-responder) at Week 8 is unclear and debatable.

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3.1.3.2 Statistical Comment 1a

Subgroup analyses for clinical remission at Week 8 in the integrated (DB data from Study M06-826 and Study M06-827, IAS-E Analysis Set) should be considered to be post-hoc and exploratory.

As seen from results from subgroup analysis for clinical remission at Week 8 in the integrated (DB data from Study M06-826 and Study M06-827, IAS-E Analysis Set), At Week 8, all subgroup analyses showed positive treatment effects. But treatment differences achieved statistical significance for CRP <10 mg/L, no Aazathioprine/6-mercaptopurine use, Aminosalicylate use, and no prior anti-TNF use.

The cut-off for CRP at baseline was pre-specified as (<10mg/L vs. ≥10mg/L). The median CRP value used by the sponsor as cut-off was not clinically justified and mainly hypothesis generating.

As seen from results from subgroup analysis for clinical remission at Week 52 for subgroup for CRP at baseline of in the Study M06-827), at Week 52 treatment difference achieved statistical significance for CRP <median at baseline, but for CRP ≥ median , it failed to achieve statistical significance.

As seen from the reviewer's tables below, at Week 8 and Week 52, treatment differences achieved statistical significance for CRP < 10 mg/L at baseline, but for CRP ≥10mg/L, they failed to achieve statistical significance. However, it should be kept in mind that these subgroup analyses were not powered to show statistical significance.

Remission per Mayo Score at Week 8
Study M06-827

Subgroup	Placebo Rate	Adalimumab Rate	95% CI
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	(0.0%, 15.2%)
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	(-3.0%, 13.1%)

Remission per Mayo Score at Week 52
Study M06-827

Subgroup	Placebo Rate	Adalimumab Rate	95% CI
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	(1.4%, 16.2%)
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	(-8.4%, 16.9%)

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3.1.3.3 Statistical Comment 2a

For early drop-outs, the design of Study M06-827 permitted subjects who had an inadequate clinical response to DB treatment to move to OL adalimumab starting at Week 12 of the study.

There was disproportionate subject who completed DB. Less placebo subjects who completed DB as compared to adalimumab (56/260 vs. 82/258, p=0.0084). With less than a third (23% for placebo and 33% for adalimumab) subjects who completed DB, the results from the remission rate at week 52 might not be reliable and trustworthy.

For the first ranked secondary endpoint of sustained clinical remission at Weeks 8 and 52, the sponsor used alternative methodology of logistic regression with treatment group as the factor. Based on this analysis, the statistical significance remained ($P = 0.048$).

It is unclear whether the anti-TNF was included as covariate in the sponsor's logistic regression analysis. The sponsor failed to provide the detailed results. It is unclear how the goodness of fit was.

Furthermore, logistic regression method involves statistical models. Koch, G and Sollecito (1984) stated these methods are advantageous in explaining the role of treatment differences in the variation of response variable. These methods, however, usually require additional non-statistical arguments to justify assumptions that the data under study are like a statistically random sample; since centers and patients in most studies are selected for inclusion by convenience, the fundamental assumptions for modeling methods are debatable.

Furthermore, there was disproportionate missing data for subjects for sustained remission per Mayo score at week 8 and week 52. More placebo subjects had missing data for sustained remission per Mayo score at week 8 and week 52 as compared to adalimumab (204/260 vs. 169/258, p=0.0010). With more than 70% missing at Week 8 and Week 52, the results from sustained remission rate at week 8 and week 52 might not be reliable and trustworthy.

For multiple imputation (MI) methodology, MI has been shown to generate less biased estimate with more statistical efficiency. However, MI will generate valid results when the underlying pattern of missing is "ignorable." Such a situation exists when data are either missing completely at random (MCAR) or missing at random (MAR). But, in the most cases of clinical trials, missing data are "non-ignorable," results from MI tends to be in favor of test drug when there was disproportionate missing data.

3.1.3.4 Statistical Comment 2b

Study M06-826 and Study M06-827 had similar design but the study populations were different. Subgroup analyses should be performed individually for each study. For evaluating treatment difference, those two studies should not be just pooled and should be combined using DerSimonian and Laird method.

3.1.3.5 Statistical Comment 2c

In the infliximab Phase 3 study design, remitters or responders were not re-randomized. However, the treatment differences for infliximabe 5 mg vs. placebo were considered to be overwhelming strong (25% for clinical remission at Week 8; 17.2% for clinical remission at Week 30; and 14.8% for sustained clinical remission (i.e., in clinical remission at both Week 8 and Week 30).

3.1.3.6 Reviewer's Comments on Sponsor's Analysis of Hospitalization and Colectomy

The integrated analysis for assessing the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy in the pooled Study M06-826 and Study M06-827 trials was a post-hoc exploratory analysis.

Results from a post-hoc study should be re-confirmed by performing a prospectively designed study.

3.1.4 Reviewer's Comments on GIDAC Votes

3.1.4.1 DISCUSSION: Please discuss the factors that you consider in defining the term "**clinically meaningful benefit**" in patients with moderately to severely active UC.

Panel members failed to agree on the magnitude of a clinical meaningful difference. They commented that the factors to be considered include measures how a patient functions, feels, survives, duration of treatment effect, and the steroid sparing effects of the treatment, length of therapy, and convenience of dosing.

3.1.4.2 <u>Clinical Remission at Week 8</u>:

VOTE: Do the observed treatment differences (Humira 160/80/40 versus placebo) in the proportion of patients that had clinical remission at Week 8 of **9.3%** (95% CI: 0.8%, 17.9%) (Study 826) and **7.2%** (95% CI: 1.3%, 13.2%) (Study 827) represent a clinically meaningful benefit? (Please explain your vote)

YES: 15 **NO: 1** **ABSTAIN: 1**

Panel members who voted "Yes" commented that they would like to have adalimumab as a treatment option in terms of unmet need, compliance, and convenience, even the observed treatment difference was small.

Panel members who voted "No" or "Abstain" agree with this reviewer that there was inadequate information on durability of response and safety. The benefit is considerably small when compared to Remicade.

The lack of robustness of the data was not discussed.

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3.1.4.3 Clinical Remission at Week 52:

(i) **VOTE:** Does having clinical remission at Week 52 represent a clinically meaningful endpoint? (Please explain your vote)

YES: 16 **NO: 1** **ABSTAIN: 0**

Panel members who voted "Yes" commented that Week 52 as a marker for durability of effect is clinically meaningful endpoint.

The panel member who voted "No" agreed with this reviewer that it is difficult to conduct a 52-Week trial.

(ii) **VOTE:** Does the observed treatment difference in the proportion of patients that had clinical remission at Week 52 of **8.8%** (95% CI: 2.9%, 14.8%) (Study 827) represent a clinically meaningful benefit? (Please explain your vote)

YES: 15 **NO: 1** **ABSTAIN: 1**

Most panel members who voted "yes" agreed that the result is clinically relevant at Week 52.

Panel member who voted "No" agreed with this reviewer that the data does not represent clinical meaningful benefit and is not confident in the interpretation of the data at Week 52.

Panel member who voted "Abstain" agreed with this reviewer that the value of 8.8% might not be real.

Missing data at Week 52 was discussed. Only 2 of 17 panel members agreed with the reviewer that the data at Week might not be reliable due to more than 60% data missing.

3.1.4.4 Clinical Remission at Both Weeks 8 and 52:

VOTE: Does the observed treatment difference in the proportion of patients that had clinical remission at both Weeks 8 and 52 of **4.4%** (95% CI: 0.1%, 9.0%) (Study 827) represent a clinically meaningful benefit? (Please explain your vote)

YES: 10 **NO: 6** **ABSTAIN: 1**

The majority of panel members commented the magnitude of treatment effect is small, but does seem clinically meaningful given the subset of patients who were difficult to treat.

Panel members who voted "No" agreed with this reviewer that the value of 4.4% for durability is very low with unknown safety concerns about missing data.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

On January 25, 2011, the sponsor submitted a supplemental Biologics License Application (BLA) consisting of two adequate and well-controlled studies (M06-826 and M06-827) and an open-label safety study (M10-223) to support the indication.

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Study M06-826, was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Study M06-827, was entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Results from Studies M06-826 and M06-827 have been statistically reviewed. The original Statistical Review and Evaluation for this sBLA was documented on October 28, 2011. A Complete Response Letter was issued for this sBLA on November 21, 2011. The statistical issues involved in CR Letter are listed below.

1. STUDY M06-826

   a. Statistical results from analysis of secondary endpoints (including clinical response) failed to show evidence of treatment benefit of adalimumab 160/80/40 over placebo. Inconsistent treatment effects were also shown in the subgroup analysis based on CRP, 10.0 mg/L vs. CRP ~10.0 mg/L (13.4% vs. -4.5%).

2. STUDYM06-827

   a. For Study M06-827, although the clinical remission rates at Weeks 8 and 52 individually showed statistical significance, the comparison of the key secondary endpoint (sustained clinical remission, i.e., remission at both Week 8 and Week 52) showed marginal significance (4.1% vs. 8.5%, p = 0.047) in favor of adalimumab. However, the significance of this result is sensitive to alternative analyses (e.g., Fishers exact test, p=0.062) and may not be reliable due to missing data. For both this endpoint and the Week 52 co-primary endpoint, there were large numbers of early drop-outs, 78% placebo vs. 69% adalimumab. These high rates undermine reliance on the estimated treatment effect, and the higher placebo rate would tend to produce bias in favor of the study drug.

   b. A subgroup analysis based on use of azathioprine or 6-mercaptopurine at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1 % vs. 12.1 %.

   c. A study design intending to show maintenance of clinical remission should re-randomize subjects who obtain remission at Week 8. Thus the study population characteristic (being in remission) is properly randomized, and those still in remission at Week 52 would serve as the primary endpoint. The sponsor's key secondary endpoint (response at Week 8 and at Week 52) reflects a measure of durability in contrast to maintenance.

The sponsor's resubmission included new analyses addressing the statistical issues included in Complete Response Letter. These analyses are generally supportive of the treatment effect as observed in the studies; however, the analyses should be considered exploratory and do not alleviate the main statistical concerns as raised in the CR letter.

The sponsor also submitted the Hospitalization Report entitled, "Effects of Adalimumab Maintenance Therapy on the Risk of Hospitalization and Colectomy in Patients with Ulcerative Colitis: Results from an Analysis of 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies of the Human Anti-TNF Monoclonal Antibody Adalimumab for Induction and Maintenance of Clinical Remission in Patients with Moderately to Severely Active Ulcerative Colitis (Study M06-826 and Study M06-827)."

The sponsor's resubmission included alternative analyses for remission rate at Week 8 for Study M06-826 and for subgroup analyses for clinical remission at Week 8 for Study M06-826 and Study M06-827. These analyses were exploratory.

For sponsor's analysis of hospitalization and colectomy, the integrated analysis for assessing the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy in the pooled Study M06-826 and Study M06-827 trials was a post-hoc analysis.

Results from post-hoc or exploratory analyses intending to show treatment benefit should be confirmed in a prospectively designed study.

4.2 Conclusions and Recommendations

The sponsor's resubmission included alternative analyses for remission rate at Week 8 for Study M06-826 and for subgroup analyses for clinical remission at Week 8 for Study M06-826 and Study M06-827. These analyses are supportive of the observed treatment effect but should be considered exploratory.

For sponsor's analysis of hospitalization and colectomy, the integrated analysis for assessing the effect of adalimumab maintenance therapy on the risk of all-cause hospitalization, UC-related hospitalization, UC- or drug-related hospitalization, and colectomy in the pooled Study M06-826 and Study M06-827 trials should be considered hypothesis generating.

5. APPENDIX

Table 1. Number and Percent of Subjects with Remission per Mayo Score at Week 8 by Mayo Score Categories (Quartile) at Baseline (Intent-to-Treat (A3) Analysis Set)

NUMBER AND PERCENT OF SUBJECTS WITH REMISSION (NRI) PER MAYO SCORE AT WEEK 8 BY MAYO SCORE CATEGORIES (QUARTILE) AT BASELINE
(INTENT-TO-TREAT(A3) ANALYSIS SET)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 25TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 25TH PERCENTILE (8) AND < MEDIAN (9)	(N=19)	(N=24)	
YES	4 (21.1)	5 (20.8)	
NO	15 (78.9)	19 (79.2)	
DIFFERENCE IN PROPORTION[B]		-0.2	
95% CONFIDENCE INTERVAL[C]		(-24.7, 24.3)	
>= MEDIAN (9) AND < 75TH PERCENTILE (10)	(N=27)	(N=33)	
YES	3 (11.1)	5 (15.2)	
NO	24 (88.9)	28 (84.8)	
DIFFERENCE IN PROPORTION[B]		4.0	
95% CONFIDENCE INTERVAL[C]		(-13.0, 21.1)	
>= 75TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

NOTE: REMISSION WAS DEFINED AS MAYO SCORE <= 2 WITH NO SUBSCORE > 1.
[A] THE BASELINE MAYO SCORE PERCENTILES WERE BASED ON ALL ITT(A3) SUBJECTS.
[B] DIFFERENCE IN PROPORTION = (ACTIVE TREATMENT GROUP - PLACEBO).
[C] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ACTIVE TREATMENT GROUP AND PLACEBO WAS BASED ON NORMAL APPROXIMATION TO THE BINOMIAL DISTRIBUTION.
@ P-VALUE IS FROM COCHRAN-MANTEL-HAENSZEL TEST ADJUSTING FOR BASELINE MAYO SCORE CATEGORIES (QUARTILE).
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Program Source Code: /zhouqx/SDA/Humira/UC/Regulatory_Req/Re_Submission/PCMS_RUN/T21106_qt_ap.sas

Reference ID: 3192233

Table 2. Number and Percent of Subjects with Remission per Mayo Score at Week 8 by Mayo Score Categories (Tertile) at Baseline
(Intent-to-Treat (A3) Analysis Set)

NUMBER AND PERCENT OF SUBJECTS WITH REMISSION (NRI) PER MAYO SCORE AT WEEK 8 BY MAYO SCORE CATEGORIES (TERTILE) AT BASELINE
(INTENT-TO-TREAT(A3) ANALYSIS SET)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.034*
< 33TH PERCENTILE (8)	(N=37)	(N=28)	
YES	3 (8.1)	7 (25.0)	
NO	34 (91.9)	21 (75.0)	
DIFFERENCE IN PROPORTION[B]		16.9	
95% CONFIDENCE INTERVAL[C]		(-1.4, 35.2)	
>= 33TH PERCENTILE (8) AND < 67TH PERCENTILE (10)	(N=46)	(N=57)	
YES	7 (15.2)	10 (17.5)	
NO	39 (84.8)	47 (82.5)	
DIFFERENCE IN PROPORTION[B]		2.3	
95% CONFIDENCE INTERVAL[C]		(-12.0, 16.7)	
>= 67TH PERCENTILE (10)	(N=47)	(N=45)	
YES	2 (4.3)	7 (15.6)	
NO	45 (95.7)	38 (84.4)	
DIFFERENCE IN PROPORTION[B]		11.3	
95% CONFIDENCE INTERVAL[C]		(-0.8, 23.4)	

NOTE: REMISSION WAS DEFINED AS MAYO SCORE <= 2 WITH NO SUBSCORE > 1.
[A] THE BASELINE MAYO SCORE PERCENTILES WERE BASED ON ALL ITT(A3) SUBJECTS.
[B] DIFFERENCE IN PROPORTION = (ACTIVE TREATMENT GROUP - PLACEBO).
[C] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ACTIVE TREATMENT GROUP AND PLACEBO WAS BASED ON NORMAL APPROXIMATION TO THE BINOMIAL DISTRIBUTION.
@ P-VALUE IS FROM COCHRAN-MANTEL-HAENSZEL TEST ADJUSTING FOR BASELINE MAYO SCORE CATEGORIES (TERTILE).
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Program Source Code: /zhouqx/SDA/Humira/UC/Regulatory_Req/Re_Submission/PCMS_RUN/T21106_tertile_ap.sas

Reference ID: 3192233

Table 3. Number and Percent of Subjects with Remission per Mayo Score at Week 8 by Mayo Score (< Median, ≥ Median) at Baseline
(Intent-to-Treat (A3) Analysis Set)

NUMBER AND PERCENT OF SUBJECTS WITH REMISSION (NRI) PER MAYO SCORE AT WEEK 8 BY MAYO SCORE (< MEDIAN, >= MEDIAN) AT BASELINE
(INTENT-TO-TREAT(A3) ANALYSIS SET)

BASELINE MAYO SCORE [A] REMISSION AT WEEK 8	PLACEBO n (%)	ADA 160/80/40 MG n (%)	P-VALUE @
			0.028*
< MEDIAN (9)	(N=56)	(N=52)	
YES	7 (12.5)	12 (23.1)	
NO	49 (87.5)	40 (76.9)	
DIFFERENCE IN PROPORTION[B]		10.6	
95% CONFIDENCE INTERVAL[C]		(-3.8, 24.9)	
>= MEDIAN (9)	(N=74)	(N=78)	
YES	5 (6.8)	12 (15.4)	
NO	69 (93.2)	66 (84.6)	
DIFFERENCE IN PROPORTION[B]		8.6	
95% CONFIDENCE INTERVAL[C]		(-1.2, 18.5)	

NOTE: REMISSION WAS DEFINED AS MAYO SCORE <= 2 WITH NO SUBSCORE > 1.
[A] THE BASELINE MAYO SCORE PERCENTILES WERE BASED ON ALL ITT(A3) SUBJECTS.
[B] DIFFERENCE IN PROPORTION = (ACTIVE TREATMENT GROUP - PLACEBO).
[C] CONFIDENCE INTERVAL FOR DIFFERENCE IN REMISSION RATES BETWEEN ACTIVE TREATMENT GROUP AND PLACEBO WAS BASED ON NORMAL APPROXIMATION TO THE BINOMIAL DISTRIBUTION.
@ P-VALUE IS FROM COCHRAN-MANTEL-HAENSZEL TEST ADJUSTING FOR BASELINE MAYO SCORE CATEGORIES (< MEDIAN, >= MEDIAN).
***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVEL, RESPECTIVELY.

Program Source Code: /zhouqx/SDA/Humira/UC/Regulatory_Req/Re_Submission/PCMS_RUN/T21106_median_ap.sas

Reference ID: 3192233

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/s/

MICHAEL E WELCH on behalf of MILTON C FAN
09/24/2012

MICHAEL E WELCH
09/24/2012
See TL review memo.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125057/0035
Drug Name:	Humira (adalimumab)
Indication(s):	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
Applicant:	Abbott Laboratories
Received Date(s):	January 26, 2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Milton C. Fan, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Division Director	Steve Wilson, Dr. PH.
Medical Division:	Gastroenterology and Inborn Errors Drug Product (DGIEP)
Clinical Team:	Aisha Peterson Johnson, M.D. (DGIEP)
Project Manager:	Kevin Bugin (DGIEP)

Keywords: clinical study, biological product, sensitivity analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study M06-826

For Study M06-826, the clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031). This treatment difference (9.3%) might not be considered clinically significant, compared to the other approved biological products. Additionally, the statistical significance of the treatment difference was sensitive to alternative analyses., and the conclusions for this study may not be considered robust from a statistical perspective.

Statistically significant differences were found across treatment groups for Mayo score at baseline.This reviewer's post-hoc analysis showed that the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score. (p=0.089).

Furthermore, the results from analysis of secondary endpoints (including clinical response) failed to show any treatment benefit of adlimumabl 160/80/40 over placebo. In the CRP subgroup analysis, an inconsistent treatment effect was shown, (13.4% for CRP < 10.0 mg/L vs. -4.5% for CRP ≥ 10.0 mg/L) (Breslow-Day, p=0.084).

Study M06-827

For Study M06-827, the clinical remission rates per Mayo score at both Week 8 and Week 52 in the adalimumab 160/80/40 treatment group were statistically higher than that in the placebo group (16.5% vs. 9.3% at Week 8, p=0.019 and 17.3% vs. 8.5% at Week 52, p=0.004). However, these treatment differences might not be considered clinically significant, compared to the other approved biological products.

The key secondary endpoint (sustained clinical remission at both Week 8 and Week 52) showed statistical significance (8.5% vs. 4.1%, p=0.047). However, the sponsor failed to re-randomize subjects for this maintenance phase of this study, as per request by the medical division at the end of phase 2 meeting.

For Study M06-827, subgroup analysis based on use of Azathioprine or 6-MP use at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% for yes vs. 12.1% for no (Breslow-Day, p=0.017).

There was disproportionate missing data for subjects for remission per Mayo score at Week 52. More placebo subjects had missing data for remission per Mayo score at Week 52 as compared to adalimumab (202/260 vs. 176/258, p=0.015). Therefore the sponsor's

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ITT analysis with NRI imputation would tend to be biased in favor of adalimumab. With more than 70% of subjects with missing data at Week 52, the treatment group difference in remission rate at Week 52 would not be reliable.

Similarly, there was disproportionate missing data for subjects for sustained remission per Mayo score at both Week 8 and Week 52. More placebo subjects had missing data for sustained remission per Mayo score at Week 8 and Week 52 as compared to adalimumab (204/260 vs. 176/258 ; p=0.001). Therefore the sponsor's ITT analysis with NRI imputation would tend to be biased in favor of adalimumab. With more than 70% of subjects with missing data at both Week 8 and Week 52, the treatment group difference in sustained remission rate at Week 8 and Week 52 would not be reliable.

Furthermore, the sponsor's result on sustained remission per Mayo score at both Week 8 and Week 52 is marginally statistically significant and thus method dependent. The treatment group difference would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.062). Therefore, the results from analysis of sustained remission per Mayo score at both Week 8 and Week 52 might not be considered robust.

1.2 Brief Overview of Clinical Studies

1.2.1 Study M06-826

This was a multicenter Phase 3 trial designed to evaluate the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with moderately to severely active UC. The study consisted of a randomized, double-blind, placebo-controlled period (DB Period) followed by an open-label period (OL Period).

The primary efficacy analysis was conducted on the data set from the DB Period through Week 8.

The objective of this study was to assess the efficacy and safety of two dosing regimens of adalimumab for the induction of clinical remission in subjects with moderately to severely active ulcerative colitis.

In addition, supportive information was collected on the maintenance of clinical remission during the open-label period of the study.

Adult subjects with moderate to severe active UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy were eligible to be enrolled.

Subjects enrolled in the study under the original protocol or Amendments 1 and 2 were randomized in a 1:1 ratio to receive adalimumab or placebo during the 12-week DB induction period. Subjects received 160 mg of adalimumab or placebo at Baseline; 80 mg adalimumab or placebo at Week 2; and 40 mg adalimumab or placebo at Weeks 4 and 6.

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At Week 8, subjects randomized to placebo received 160 mg adalimumab followed by 80 mg adalimumab at Week 10. Subjects randomized to adalimumab continued to receive 40 mg adalimumab at Weeks 8 and 10. All subjects continued to receive 1 injection of open-label (OL) adalimumab 40 mg eow beginning at Week 12 up to Week 52 (or the ET visit).

The primary efficacy endpoint of this study is the proportion of subjects with remission at Week 8.

The study enrolled 576 subjects, including 186 subjects under the original protocol and protocol Amendments 1 and 2, and 390 subjects under protocol Amendments 3 and 4. Analyzed: 576 subjects (safety); 575 subjects (efficacy [ITT-E Set]), 390 subjects (efficacy [ITT-A3 Set]).

1.2.2 Study M06-827

This study was a multicenter, randomized, double-blind, placebo controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis

The primary objective of this study was to assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis (UC). The secondary objective of this study was to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration.

Subjects at least 18 years of age with moderately to severely active UC (Mayo score of 6 to 12 points and an endoscopy subscore of 2 to 3 points), despite concurrent treatment with corticosteroids and/or immunosuppressants) confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, were to be enrolled at approximately 120 sites worldwide.

The duration of the study was up to 65 weeks, including a Screening Period of up to 3 weeks, a double-blind (DB), placebo-controlled treatment period of up to 52 weeks, and a 70 day follow-up phone call for subjects who prematurely discontinued or who did not enroll in the extension study (Study M10 223).

Subjects were to be stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomized in a 1:1 ratio to receive adalimumab or placebo by SC injection.

The ranked co-primary efficacy endpoints were:
- The proportion of subjects who achieved remission at Week 8 and
- The proportion of subjects who achieved remission at Week 52.

A total of 518 subjects were randomized into the study at 103 sites in the US, Canada, Austria, Belgium, Denmark, France, Germany, Israel, Norway, Portugal, Spain,

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Switzerland, the Czech Republic, Hungary, Poland, Australia, and New Zealand. The number of subjects per site ranged from 1 to 22. One subject randomized to adalimumab did not receive study drug. Of the 518 subjects who entered the study, 24 subjects (14 randomized to adalimumab and 10 to placebo) from 3 sites (Dr. Wild's [22635], Dr. Roeder's [36809], and Dr. Kellner's [27010] sites) were excluded from the ITT analysis due to site noncompliance.

1.3 Statistical Issues and Finding

Study M06-826

For Study M06-826, in the ITT-A3 set the clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was statistically higher than that in the placebo group (18.5% vs. 9.2%). However, the treatment difference was borderline (p=0.0471; Fisher's exact test) and was not robust.

There was no statistically significant difference in clinical remission observed between the adalimumab 80/40 treatment group and the placebo group (p=0.833).

This reviewer performed a post-hoc analysis of the proportion of subjects with remission at Week 8 controlling for Mayo score at baseline using the Cochran-Mantel-Haenszel method. The results revealed that the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score. (p=0.0892).

The sponsor stated in Response to Information Request dated May 09, 2011 that due to windowing rules for dosing (±3 days), one subject in adalimumab 160/80/40 had a response attributed to Week 8 in the Observed Case analysis but did not receive the Week 8 dose of adalimumab (i.e., was not a completer). This subject was considered as a responder in the sponsor's analysis of primary efficacy endpoint: proportion of subjects with remission at Week 8. So, the status of this subject (responder or non-responder) is debatable.

This reviewer performed the sensitivity analyses to find out how many alternation in the responder status would change 2-sided p-value from the observed p-value to greater than 0.05, keeping sample sizes fixed.

These sensitivity analysis revealed that this study could be a "negative" study, if a change in the responder status of 1 subjects in the adalimumab 160/80/40 group from responder to non-responder , or in the responder status of just 1 placebo subject from non-responder to responder.

In the pre-sBLA meeting dated November 23, 2010, the medical division recommends that the post hoc analysis utilize a definition of clinical remission as total Mayo score ≤ 2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability) and no individual subscore > 1.

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However, the sponsor failed to perform the statistical analysis for FDA definition of clinical remission in the submission.

This reviewer performed the post-hoc analysis for FDA definition of clinical remission at Week 8. Te new FDA defined clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was numerically higher than that in the placebo group; but, it failed achieved statistical significance. (11.5% vs. 4.6%, p=0.067, Fisher's Exact test).

Furthermore, the results from analysis of secondary endpoints failed to show any statistical significant treatment benefit of adlimumabl 160/80/40 over placebo. Moreover, subgroup analysis based on the CRP showed inconsistent findings. The treatment difference in clinical remission at Week 8 between adalimumab 160/80/40 and placebo was 13.4% for CRP < 10.0 mg/L vs. -4.5% for CRP ≥10.0 mg/L, (Breslow-Day, p=0.0839).

Study M06-827

For Study M06-826, the clinical remission rates per Mayo score at both Week 8 and Week 52 in the adalimumab 160/80/40 treatment group were statistically higher than that in the placebo group (16.5% vs. 9.3% at Week 8 and 17.3% vs. 8.5% at Week 52).

The sponsor failed to re-randomize subjects for maintenance phase of this study, as per request by the medical division at phase II meeting.

For Study M06-827, subgroup analysis based on Azathioprine or 6-MP use at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% for yes vs. 12.1% for no (Breslow-Day, p=0.0175).

There was disproportionate missing data for subjects for remission per Mayo score at Week 52. More placebo subjects had missing data for remission per Mayo score at Week 52 as compared to adalimumab (202/260 vs. 176/258, p=0.0152). Therefore the sponsor's ITT analysis with NRI imputation tends to be biased in favor of adalimumab. With more than 70% subjects with missing data at Week 52, the treatment group difference in remission rate at Week 52 might not be reliable and trustworthy.

There was disproportionate missing data for subjects for sustained remission per Mayo score at Week 8 and Week 52. More placebo subjects had missing data for sustained remission per Mayo score at Week 8 and Week 52 as compared to adalimumab (204/260 vs. 169/258 ; p=0.0010). Therefore the sponsor's ITT analysis with NRI imputation tends to be biased in favor of adalimumab. With more than 70% subjects with missing data at Week 8 and Week 52, the treatment group difference in sustained remission rate at Week 8 and Week 52 might not be reliable and trustworthy.

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This reviewer performed the post-hoc analyses for new FDA definition of clinical remission at Week 8, Week 52, and Week 8 and Week 52. For the FDA defined clinical remission, the treatment difference achieved statistical significance at nominal significance level of 0.05 at Week 8 and at Week 52. But, it failed to achieve significance at minor p-value 0.05 at Week 8 and Week 52 (p=0.088).

Furthermore, the sponsor's result on sustained remission per Mayo score at Week 8 and Week 52 is method dependent. The treatment group difference would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.0621). Therefore, the results from analysis of sustained remission per Mayo score at Week 8 and Week 52 might not be considered robust.

2. INTRODUCTION

2.1 Overview

The sponsor has submitted two adequate and well-controlled studies (M06-826 and M06-827) and an open-label safety study (M10-223) for the claim.

Study M06-826, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Study M06-827, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

Interim results from Study M10-223, entitled "A Multicenter, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects with Ulcerative Colitis"

2.2 Data Sources

The electronic submission was located at:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx>

The sponsor submitted response to request for information eCTD sequence 0070 dated May 27, 2011 for the Information Request by this reviewer dated May 9, 2011.

The sponsor submitted response to request for information eCTD sequence 0082 dated July 27, 2011 for the Information Request by this reviewer dated July 12, 2011.
The sponsor submitted response to request for information eCTD sequence 0091 dated September 29, 2011 for the Information Request by this reviewer dated September 9, 2011.

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study M06-826

3.1.1.1 Study Design

This was a multicenter Phase 3 trial designed to evaluate the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with moderately to severely active UC. The study consisted of a randomized, double-blind, placebo-controlled period (DB Period) followed by an open-label period (OL Period).

The primary efficacy analysis was conducted on the data set from the DB Period through Week 8.

The objective of this study was to assess the efficacy and safety of two dosing regimens of adalimumab for the induction of clinical remission in subjects with moderately to severely active ulcerative colitis.

In addition, supportive information was collected on the maintenance of clinical remission during the open-label period of the study.

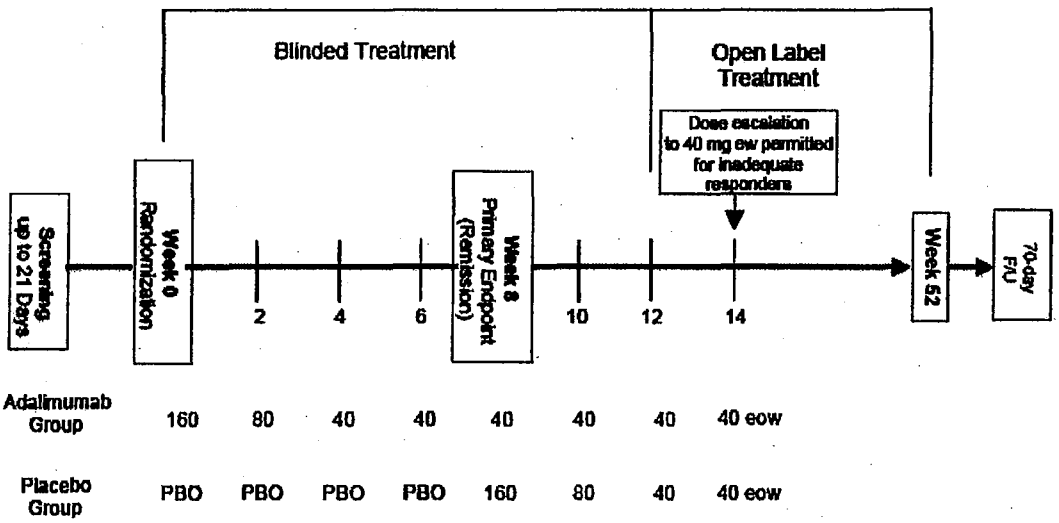
Adult subjects with moderate to severe active UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or by flexible sigmoidoscopy with biopsy were eligible to be enrolled.

Subjects enrolled in the study under the original protocol or Amendments 1 and 2 were randomized in a 1:1 ratio to receive adalimumab or placebo during the 12-week DB induction period. Subjects received 160 mg of adalimumab or placebo at Baseline; 80 mg adalimumab or placebo at Week 2; and 40 mg adalimumab or placebo at Weeks 4 and 6. At Week 8, subjects randomized to placebo received 160 mg adalimumab followed by 80 mg adalimumab at Week 10. Subjects randomized to adalimumab continued to receive 40 mg adalimumab at Weeks 8 and 10. All subjects continued to receive 1 injection of open-label (OL) adalimumab 40 mg eow beginning at Week 12 up to Week 52 (or the ET visit).

A schematic of the study design prior to Amendment 3 was shown in Figure 1.

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Figure 1. Study Design Schematic Prior to Amendment 3



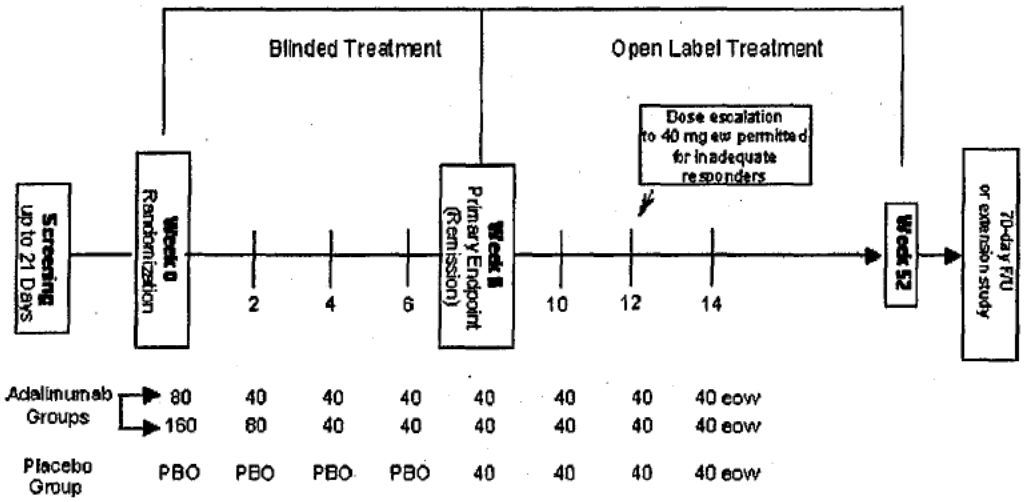
In August 2007, the study design was amended to incorporate an additional adalimumab induction dosing arm of 80/40 mg. Earlier that year, both 160/80/40 mg and 80/40 mg induction regimens had been approved in the EU as induction treatment for (Crohn's disease) CD. The adalimumab induction dosing regimen of 80/40 mg was therefore included so that both of these approved induction regimens would be evaluated for the induction of remission of UC.

Subjects enrolled in the study after Amendment 3 were randomized in a 1:1:1 ratio to receive 1 of 2 induction regimens of adalimumab or placebo during the 8-week DB induction period. Subjects received DB therapy from Baseline until Week 8 and OL therapy from Week 8 until the end of the study. In the first adalimumab DB induction dosing arm (adalimumab 160/80/40), subjects received 4 injections of adalimumab 40 mg (160 mg) at Baseline followed by 2 injections of adalimumab 40 mg (80 mg) at Week 2. Subjects in the second adalimumab dosing arm (adalimumab 80/40) received 2 injections of adalimumab 40 mg (80 mg) and 2 injections of placebo at Baseline followed by 1 injection of adalimumab 40 mg and 1 injection of placebo at Week 2. Subjects randomized to placebo received 4 injections of placebo at Baseline followed by 2 injections of placebo at Week 2. Subjects randomized to receive adalimumab induction dosing received 1 injection of adalimumab 40 mg at Week 4 and Week 6, while subjects randomized to placebo received 1 injection of placebo at these corresponding times. Beginning at Week 8, but after the Week 8 study assessments had been completed, all subjects received 1 injection of OL adalimumab 40 mg eow until Week 52 or early termination. Starting at Week 12, subjects who had inadequate responses to treatment (as defined using partial Mayo scores were permitted to dose escalate to adalimumab 40 mg weekly. Subjects with persistent inadequate response while on weekly treatment could be discontinued from the study at the discretion of the investigator.

A schematic of the study design implemented by Amendment 3 shown in Figure 2.

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Figure 2. Study Design Schematic Following Protocol Amendment 3



The key differences in study design before and after Amendment 3 are given below.

Table 10. Key Differences in Study Design Before and After Amendment 3

Prior to Amendment 3	After Amendment 3
Two treatment arms: Placebo Adalimumab 160/80/40	Three treatment arms: Placebo Adalimumab 80/40 Adalimumab 160/80/40
Double-blind period lasting for 12 weeks.	Double-blind period lasting for 8 weeks.
Stable (± 5 mg) corticosteroid dose (prednisone of ≥ 20 mg/day or equivalent) for at least 14 days prior to Baseline or maintenance corticosteroid dose (prednisone of ≥ 10 mg/day and < 20 mg/day or equivalent) for at least 40 days prior to Baseline.	Subjects had to be stable on prednisone ≥ 20 mg/day or equivalent for at least 14 days prior to Baseline; for doses of prednisone < 20 mg/day or equivalent, subjects had to be stable for at least 40 days prior to Baseline.
Prior and concurrent infliximab or anti-TNF excluded.	All prior and concurrent biologics excluded (including infliximab and anti-TNFs).
Immunosuppressants other than azathioprine or 6-MP (e.g., cyclosporine, methotrexate, or tacrolimus) prohibited within 60 days prior to Baseline and during the study.	Cyclosporine, tacrolimus, mycophenolate mofetil, and investigational agents prohibited 30 days or 5 half-lives prior to Baseline and during the study. Intravenous corticosteroid use prohibited within 14 days prior to Screening, during the Screening Period, and during the study.

The definitions of efficacy-related measures are given below.

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Table 4. Definitions of Efficacy-Related Measures

Term	Definition
Mayo score	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), rectal bleeding (0 – 3), physician's global assessment (0 – 3) and endoscopy (0 – 3). This score ranges from 0 to 12 points with higher scores representing more severe disease.
Partial Mayo score	Composite score of UC disease activity based on the subscores of stool frequency, rectal bleeding, and physician's global assessment and DOES NOT include the endoscopy subscore. This score ranges from 0 to 9 points.
Clinical response	A decrease in Mayo Score of ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1.
Inadequate responder	• Subject with a Baseline Partial Mayo Score of 4 to 7 who presents with a Partial Mayo Score greater than or equal to their Baseline score on two consecutive visits at least 14 days apart. • Subject with a Baseline Partial Mayo Score of 8 or 9 who presents with a Partial Mayo Score ≥ 7 on two consecutive visits at least 14 days apart.
Clinical remission	Mayo Score ≤ 2 with no subscore > 1.

* See Appendix E of the protocol for more information about the Mayo scoring system.

All subjects were to be provided with a Subject Diary at the Screening Visit to record UC-related symptoms. The subject diary was to provide information on the subject-reported subscores for calculating the partial Mayo score at each visit beginning at Baseline. The worst diary entry from the 3 days prior to each study visit was to be used for each subject-reported subscore. The investigator was to use the subject-reported subscores of abdominal discomfort and functional assessment to determine the physician's global assessment subscore. The Mayo score (consisting of the partial Mayo score plus the endoscopy subscore) was to be calculated at study visits when an endoscopy is performed. The endoscopy subscore from the Screening visit was to be used to calculate the Mayo score at the Baseline visit.

Efficacy analyses were to be conducted in the intent-to-treat population. In the efficacy analyses, missing or incomplete data were to be handled using the non-responder imputation method. Efficacy analyses for sensitivity were also to be performed with missing or incomplete data handled as observed case and last observation carried forward (LOCF) method.

The Intent-To-Treat - A3 (ITT-A3) Population include all subjects with confirmed UC at Baseline who were randomized according to the revised study design described in Amendment 3 (and Amendment 4) and received at least 1 injection of the following induction regimens: adalimumab 160/80/40 mg, adalimumab 80/40 mg, or placebo.

The ITT-Extended (ITT-E) Population included all subjects with confirmed UC at Baseline who were randomized according to the original protocol or any of the 4 protocol amendments and received at least 1 injection of the following induction regimens: adalimumab 160/80/40 mg, adalimumab 80/40 mg, or placebo.

The following definitions were used to describe the primary and secondary variables:

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Term	Definition
Clinical Remission	Mayo score ≤ 2 with no individual subscore > 1
Clinical Response per Mayo Score	A decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
Clinical Response per Partial Mayo Score	A decrease in Partial Mayo Score ≥ 2 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore ≥ 1 or an absolute RBS of 0 or 1
IBDQ Responder	A subject with at least a 16 point increase from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score
Mucosal Healing	Endoscopy subscore of 0 or 1

The primary efficacy endpoint of this study is the proportion of subjects with remission at Week 8.

Ranked secondary efficacy variables assessed at Week 8 included (in the order at which statistical test was to be conducted):

1. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 60/80/40 versus placebo).
2. Proportion of subjects with mucosal healing at Week 8 (ADA 160/80/40 versus placebo).
3. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
4. Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
5. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
6. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 80/40 versus placebo).
7. Proportion of subjects with mucosal healing at Week 8 (ADA 80/40 versus placebo).
8. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
9. Proportion of subjects with Physician's Global Assessment subscore indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (ADA 80/40 versus placebo).
10. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (ADA 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (ADA 80/40 versus placebo).

Non-ranked secondary efficacy variables:

- Proportion of subjects with response per Partial Mayo Score at Weeks 2, 4, and 6.
- Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of subjects with Physician's Global Assessment subscore indicative of mild Disease (≤ 1) at Weeks 2, 4, and 6.
- Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at

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Weeks 2, 4, and 6.

- Change from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score at Week 8.
- Change from Baseline in Short Form-36 Questionnaire (SF-36) at Week 8.
- Change from Baseline in Partial Mayo Score at Weeks 2, 4, 6, and 8.
- Change from Baseline in Mayo Score at Week 8.
- Time to clinical response per Partial Mayo Score (up to Week 8).

The primary efficacy variable was remission rate at Week 8, which was defined as the proportion of subjects with a total Mayo score ≤ 2 and no individual subscore > 1.

The analyses were to be carried out in the following hierarchical order to handle the multiplicity issues induced by the 2 comparisons to placebo.

1. Compare the remission rates of adalimumab 160/80/40 mg group and placebo at Week 8. The superiority of adalimumab 160/80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.
2. Compare the remission rates of adalimumab 80/40 mg group and placebo at Week 8. The superiority of adalimumab 80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.

A p value ≤ 0.05 from Comparison 1 was necessary to initiate Comparison 2 at a significance level of 0.05. Since a hierarchical procedure was used, each comparison was to be tested at a significance level of 0.05 and overall alpha level of 0.05 could be preserved.

The secondary efficacy analysis was to be performed in the ITT-A3 population. The statistical comparisons for the ranked secondary endpoints were to be carried out in hierarchical order.

Statistically significant results (p value ≤ 0.05) had to be achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

1. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 160/80/40 versus placebo).
2. Proportion of subjects with mucosal healing at Week 8 (ADA 160/80/40 versus placebo).
3. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
4. Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
5. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 160/80/40 versus placebo).
6. Proportion of subjects with clinical response per Mayo score at Week 8 (ADA 80/40 versus placebo).
7. Proportion of subjects with mucosal healing at Week 8 (ADA 80/40 versus placebo).

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8. Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
9. Proportion of subjects with Physician's Global Assessment subscore indicative of "normal or mild disease" (or numerical score ≤ 1) at Week 8 (ADA 80/40 versus placebo).
10. Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1) at Week 8 (ADA 80/40 versus placebo).
11. Proportion of IBDQ responders at Week 8 (ADA 160/80/40 versus placebo).
12. Proportion of IBDQ responders at Week 8 (ADA 80/40 versus placebo).

The proportion of subjects achieving clinical response per Mayo score (yes/no), which was defined as a decrease in Mayo score of ≥ 3 points and a ≥ 30% decrease from baseline plus a decrease in the rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS of 0 or 1, was to be presented by randomized treatment group at Week 8.

Subjects with a missing Mayo score were not to be considered as achieving response.

Assuming 15% of subjects in the placebo group achieved clinical remission at Week 8, a sample size of 125 in each treatment group in the ITT-A3 population would be adequate to detect a 15% difference using a chi-square test with 80% power at a 0.05 two-sided significance level. Thus, a total of 375 subjects were to be randomized following Amendment 3 of the study.

The original protocol was amended 4 times and underwent 3 administrative changes. Changes were enacted by each global amendment.

3.1.1.2 Sponsor's Analysis

The study enrolled 576 subjects, including 186 subjects under the original protocol and protocol Amendments 1 and 2, and 390 subjects under protocol Amendments 3 and 4. Analyzed: 576 subjects (safety); 575 subjects (efficacy [ITT-E Set]), 390 subjects (efficacy [ITT-A3 Set]).

A total of 390 subjects were enrolled after Amendment 3 (ITT-A3 Set)

The disposition of subjects is given below.

Reference ID: 3200370

Table 5. Disposition of Subjects (ITT-A3 Set)

Subject Status	Number (%) of Subjects			
	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 130	Total N = 390
Completed study	91 (70.0)	86 (66.2)	95 (73.1)	272 (69.7)
Discontinued study at any time	39 (30.0)	44 (33.8)	35 (26.9)	118 (30.3)
Reasons for discontinuation[a]				
Adverse event	22 (16.9)	19 (14.6)	14 (10.8)	55 (14.1)
Withdrew consent	3 (2.3)	9 (6.9)	5 (3.8)	17 (4.4)
Lost to follow-up	0	3 (2.3)	1 (0.8)	4 (1.0)
Lack of efficacy	26 (20.0)	22 (16.9)	17 (13.1)	65 (16.7)
Protocol violation	1 (0.8)	1 (0.8)	3 (2.3)	5 (1.3)
Other[b]	0	4 (3.1)	1 (0.8)	5 (1.3)
Completed Week 8	121 (93.1)	118 (90.8)	121 (93.1)	360 (92.3)
Discontinued study prior to Week 8	9 (6.9)	12 (9.2)	9 (6.9)	30 (7.7)
Reasons for discontinuation[a]				
Adverse event	6 (4.6)	7 (5.4)	4 (3.1)	17 (4.4)
Withdrew consent	0	4 (3.1)	1 (0.8)	5 (1.3)
Lost to follow-up	0	2 (1.5)	0	2 (0.5)
Lack of efficacy	5 (3.8)	5 (3.8)	2 (1.5)	12 (3.1)
Protocol violation	0	0	2 (1.5)	2 (0.5)
Other[c]	0	0	1 (0.8)	1 (0.3)

a. Subjects could have discontinued for more than one reason.

b. Reasons for discontinuation recorded as "other" included: diagnosis of CD, loss of response, primary non-responder, UC symptoms not improving, investigator decision, subject noncompliance, positive TB skin test, subject wanted to start family, or total colectomy surgery within the 70-day follow-up period.

c. Diagnosis of CD.

As seen table above, of whom 30 (7.7%) discontinued the study before Week 8. The most frequently reported reasons for discontinuation in the ITT-A3 Set overall and among treatment groups were adverse events, lack of efficacy, and withdrawn consent.

More subjects in the adalimumab 80/40 treatment group withdrew consent than in the adalimumab 160/80/40 or placebo treatment groups.

The protocol deviations during double-blind period though Week 8 for ITT-A3 set is given below.

Reference ID: 3200370

Table 7. Protocol Deviations During DB Period Through Week 8 (ITT-A3 Set)

	Number (%) of Subjects			
Deviation Category	Placebo N = 130	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 130	Total N = 390
Inclusion/exclusion criteria deviations	8 (6.2)	9 (6.9)	8 (6.2)	25 (6.4)
Developed withdrawal criteria but was not withdrawn	0	0	1 (0.8)	1 (0.3)
Received wrong treatment or incorrect dose	10 (7.7)	10 (7.7)	11 (8.5)	31 (7.9)
Received excluded concomitant treatment	11 (8.5)	13 (10.0)	8 (6.2)	32 (8.2)

Note: Subjects could have had more than 1 deviation but are counted once in each respective category.
Cross reference: Table 14.1__2.4

The number of subjects by analysis set is summarized below.

Table 9. Number of Subjects by Analysis Set

	Number of Subjects			
Analysis Set	Placebo	Adalimumab 80/40	Adalimumab 160/80/40	Total
ITT-A3	130	130	130	390
ITT-E	222	130	223	575
Per Protocol	120	122	124	366
Safety	223	130	223	576

Cross reference: Table 14.1__1

3.1.1.2.1 Planned Analysis

The analyses for primary efficacy endpoint were to be carried out in the following hierarchical order to handle the multiplicity issues induced by the 2 comparisons to placebo.

1. Compare the remission rates of adalimumab 160/80/40 mg group and placebo at Week 8. The superiority of adalimumab 160/80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.
2. Compare the remission rates of adalimumab 80/40 mg group and placebo at Week 8. The superiority of adalimumab 80/40 mg treatment over placebo was to be established by the Chi-square test (two-sided) at an alpha level of 0.05.

A p value ≤ 0.05 from Comparison 1 was necessary to initiate Comparison 2 at a significance level of 0.05. Since a hierarchical procedure was used, each comparison was to be tested at a significance level of 0.05 and overall alpha level of 0.05 could be preserved.

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The statistical comparisons for the ranked secondary endpoints were to be carried out in hierarchical order. Statistically significant results (p value ≤ 0.05) had to be achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

The difference in proportion of subjects achieving response between adalimumab group and placebo group was to be assessed using the chi-square test, or Fisher's exact test as appropriate.

Other ranked dichotomous variables that included proportion of subjects with mucosal healing, proportion of subjects having mild disease indicated by components of the Mayo score (RBS, Physician's Global Assessment subscore (PGA) and Stool Frequency subscore), and proportion of IBDQ responders, were be analyzed using the same method used to analyze clinical response.

Non-ranked dichotomous efficacy variables will be analyzed using the same methods listed above.

Change from baseline in the IBDQ scores; SF-36 scores; Mayo score and partial Mayo score were to be summarized using descriptive statistics. The treatment difference in mean change was to be analyzed using the ANOVA model including factors of treatment and baseline scores, or non-parametric test, as appropriate. Both the data as-observed and the LOCF method could be used as appropriate.

The median time to achieve response per partial Mayo score from baseline was to be calculated using the Kaplan-Meier method.

Descriptive statistics were to be presented for the variables analyzed from the OL period of the study. The response rate based on Mayo score and the colectomy rate during the study was to be tabulated and could be tested using the chi-square test or Fisher's exact test, as appropriate.

3.1.1.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for ITT-A3 are given in Appendix Tables 1 to 3 respectively for demographic characteristics, baseline disease history, baseline disease activity, and baseline disease severity by Mayo subscore.

As seen from Appendix Tables 1 to 3, the majority of subjects in the ITT-A3 were male, white, and < 65 years old. There were no statistically significant differences across treatment groups. In the ITT-A3 Set, the DB treatment groups had comparable UC histories, although placebo subjects had a slightly lesser mean duration of disease, with a notable difference between the frequency of subjects reporting pancolitis versus UC of the descending colon. By comparison, subjects in the adalimumab treatment groups had smaller differences between pancolitis and descending colon.

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Baseline disease activity was comparable among subjects in the ITT-A3 Set. There were no statistically significant differences observed across treatment groups.

All but 1 subject (placebo, 2076564451) in the ITT-A3 Set had moderate to severe disease at Baseline (as defined by a Mayo score ≥ 6 and an endoscopy subscore ≥ 2). The majority of subjects had moderate to severe disease at Baseline as assessed by all subscores of the Mayo score in the ITT-A3 Set.

For physician's global assessment subscores in the ITT-A3 set, a greater proportion of subjects randomized to adalimumab had mild disease or severe disease compared with subjects randomized to placebo (6.9% versus 3.8% and 33.5% versus 25.4%, respectively), whereas a greater proportion of subjects randomized to placebo had moderate disease compared with subjects randomized to adalimumab (70.8% versus 59.2%, respectively).

3.1.1.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy endpoint of this study is the proportion of subjects with remission at Week 8.

The result from analysis of the proportion of subjects with remission at Week 8 is given below.

Number and Percentage of Subjects with Remission per Mayo Score at Week 8
Study M06-826
(ITT-A3 Set-NRI)

Treatment	Rate	vs. placebo Difference	vs. placebo p-value	95% C. I.
ADA 80/40	13/130 (10.0%)	0.8%	0.833	(-6.4%, 7.9%)
ADA 160/80/40	24/130 (18.5%)	9.3%	0.031	(0.9%, 17.6%)
Placebo	12/130 (9.2%)			

Compiled from Table 35.
P-values obtained from Chi-square test.
95% C.I. obtained from normal approximation by this reviewer.

As seen from table above, in the ITT-A3 set the clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was twice as high as the clinical remission rate in the placebo group; this difference was statistically significant. However, there was no statistically significant difference observed between the adalimumab 80/40 treatment group and the placebo group.

3.1.1.2.3.1 Sensitivity Analyses

The sponsor also performed sensitivity analyses for primary efficacy endpoint. Sensitivity analyses included LOCF and Per Protocol-NRI analyses. In the LOCF analysis, the last non-missing post-baseline values were carried forward.

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The results from sensitivity analyses are given below.

Sensitivity Analyses
Study M06-826
(ITT-A3 Set)

Analysis	Placebo Rate	Adalimumab 80/40 Rate	p-value[a]	Adalimumab 160/80/40 Rate	p-value[a]
LOCF	12/123 (9.8%)	13/120 (10.8%)	0.782	24/124 (19.4%)	0.033
Per Protocol-NRI	10/120 (8.3%)	12/122 (9.8%)	0.684	23/124 (18.5%)	0.020

Complied from Table 35
[a]p-values obtained from Chi-square test.

As seen from table above, similar results were seen in the PP analysis set and in the ITT-A3 set when LOCF imputation was used instead of NRI imputation.

3.1.1.2.4 Sponsor's Analysis of Secondary Efficacy Parameters

3.1.1.2.4.1 Ranked Secondary Variables

Twelve ranked secondary variables were to be tested in a hierarchical order to account for multiple testing. Statistically significant results (P value ≤ 0.05) had to be achieved for a comparison in the higher rank to initiate the next comparison in the lower rank.

Summary of results of ranked secondary endpoint for ITT-A3 set: NRI is given below.

Reference ID: 3200370

Table 37. Summary of Results of Ranked Secondary Endpoints (ITT-A3 Set; NRI)

Proportion of Subjects With:[a]	Number (%) of Subjects: Placebo N = 130	Number (%) of Subjects: Adalimumab 160/80/40 N = 130	*P* value[b]
1. Clinical response at Week 8	58 (44.6)	71 (54.6)	0.107
2. Mucosal healing at Week 8	54 (41.5)	61 (46.9)	0.382
3. RBS ≤ 1 at Week 8	86 (66.2)	101 (77.7)	0.038
4. PGA ≤ 1 at Week 8	61 (46.9)	78 (60.0)	0.035
5. SFS ≤ 1 at Week 8	49 (37.7)	63 (48.5)	0.080
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
6. Clinical response at Week 8	58 (44.6)	67 (51.5)	0.264
7. Mucosal healing at Week 8	54 (41.5)	49 (37.7)	0.526
8. RBS ≤ 1 at Week 8	86 (66.2)	91 (70.0)	0.506
9. PGA ≤ 1 at Week 8	61 (46.9)	70 (53.8)	0.264
10. SFS ≤ 1 at Week 8	49 (37.7)	47 (36.2)	0.797
	Placebo N = 130	**Adalimumab 160/80/40 N = 130**	
11. IBDQ response at Week 8	75 (57.7)	79 (60.8)	0.614
	Placebo N = 130	**Adalimumab 80/40 N = 130**	
12. IBDQ response at Week 8	75 (57.7)	70 (53.8)	0.532

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore

a. Listed in rank order, as indicated by the number preceding each endpoint variable.

b. *P* value for differences between active treatment group and placebo from chi-square test (or Fisher's exact test if ≥ 20% of the cell have an expected count < 5).

Cross reference: Tables 14.2__3.1 through 14.2__3.6

As seen from table above, ranked endpoint No. 1 (clinical response per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group versus placebo) did not meet the criteria for statistical significance.

3.1.1.3 Reviewer's Comments and Evaluation

3.1.1.3.1 Mayo Score at Baseline

It was found that there were statistically significant differences across treatment groups for Mayo score at baseline in the ITT-A3 Set (chi-square p-value 0.0044) as seen below.

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Mayo Score at Baseline
Study M06-826
(ITT-A3 Set)

Frequency Row Pct	6	7	8	9	10	11	12	Total
ADALIMUMAB 160/8 0/40 MG EOW	15 11.54	13 10.00	24 18.46	33 25.38	25 19.23	15 11.54	5 3.85	130
ADALIMUMAB 80/40 MG EOW	9 6.92	10 7.69	36 27.69	26 20.00	22 16.92	17 13.08	10 7.69	130
PLACEBO	9 6.92	28 21.54	19 14.62	27 20.77	34 26.15	8 6.15	5 3.85	130
Total	33	51	79	86	81	40	20	390

3.1.1.3.2 Remission Rate at Week 8

This reviewer performed a post-hoc analysis of the proportion of subjects with remission at Week 8 controlling for Mayo score at baseline using the Cochran-Mantel-Haenszel method.

The results are given is given below.

Mayo Score at baseline	Placebo Rate	Adalimumab 80/40 Rate	p-value[a]	Adalimumab 160/80/40 Rate	p-value[a]
6	2/9 (22.2%)	5/9 (55.6%)		5/15 (33.3%)	
7	1/28 (3.6%)	1/10 (10.0%)		2/13 (15.4%)	
8	4/19 (21.1%)	4/36 (11.1%)		5/24 (20.8%)	
9	3/27 (11.1%)	1/26 (3.9%)		5/33 (15.2%)	
10	2/34 (5.9%)	1/22 (4.6%)		3/25 (12.0%)	
11	0/8 (0.0%)	0/17 (0.0%)		3/15 (20.0%)	
12	0/5 (0.0%)	1/10 (10.0%)		1/5 (20.0%)	
Combined			0.9748		0.0852

Compiled by this reviewer.
[a]p-values obtained from Cochran-Mantel-Haenszel test.

As seen from Table above, the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score.

There was no statistically significant difference observed between the adalimumab 80/40 treatment group and the placebo group when adjusted for baseline Mayo score.

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3.1.1.3.3 Sensitivity Analyses for Primary Efficacy Endpoint

Per this reviewer's request, the sponsor had performed observed case, complete case, and multiple imputation analyses. The results of these sensitivity analyses are given below.

Sensitivity Analyses
Study M06-826
(ITT-A3 Set)

Analysis	Placebo Rate	Adalimumab 80/40 Rate	p-value[a]	Adalimumab 160/80/40 Rate	p-value[a]
Observed Case	12/121 (9.9%)	13/118 (11.0%)	0.781	24/122 (19.7%)	0.032
Complete Case	12/120 (10.0%)	13/117 (11.1%)	0.781	23/121 (19.0%)	0.047
Multiple Imputation	9.5%	10.7%	0.753	19.1%	0.028

Complied from Tables 1_1, 1_2, and 1_3.
[a]p-values obtained from Chi-square test.

As seen from table above, similar results were seen in the observed case, complete case, and multiple imputation analyses.

Three subjects (1 subject in each treatment group) were included in the observed case analysis but not in complete case analysis for remission at Week 8 because although they had Week 8 evaluations, they did not receive the Week 8 dose of adlimumab and were therefore not considered completers.

The sponsor stated in the Response to Information Request dated May 09, 2001 that due to windowing rules for dosing (±3 days), one subjects in Adalimumab 160/80/40 had a response attributed to Week 8 in the Observed Case analysis but did not receive the Week 8 dose of dalimumab (i.e., was not a completer).

Furthermore, the sponsor's result for complete case analysis might be method dependent. It would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.0665).

3.1.1.3.4 Sensitivity Analyses

The sponsor stated in the Response to Information Request dated May 09, 2011 that due to windowing rules for dosing (±3 days), one subject in Adalimumab 160/80/40 had a response attributed to Week 8 in the Observed Case analysis but did not receive the Week 8 dose of adalimumab (i.e., was not a completer). This subject was considered as a responder in the sponsor's analysis of primary efficacy endpoint: proportion of subjects with remission at Week 8.

In the Response to Information Request dated September 09, 2001, it was stated that three subjects (1 subject in each treatment group) from Study M06-826 were included in the OC (observed case) analysis but not the CC (complete case) analysis for remission at Week 8 because although they had Week 8 evaluations, they did not receive the Week 8

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dose of adalimumab and were therefore not considered completers. The subject in adalimumab 160/80/40 treatment group is as follows:

- **Subject 63951 (adalimumab 160 80/40 treatment group) was a 29-year-old male with a Baseline Mayo score of 6 who received study drug at Week 0 only and was discontinued due to a protocol violation. The subject entered the study with a Mayo score of 6 and after discontinuation the partial Mayo score at Day 54 was reported to be 0.**

So, the remission status of this subject (responder or non-responder) at Week 8 is unclear and debatable..

This reviewer performed the following sensitivity analyses to find out how many alternation in the responder status would change 2-sided p-value from the observed p-value to greater than 0.05, keeping sample sizes fixed. The results for study M06-826 are given in Appendix Table 4.

(1) In case 1, the adalimumab 160/80/40 responder rate was varied, keeping the placebo responder rate fixed at 9.2%.
(2) In case 2, placebo responder rate was varied, keeping the adalimumab 160/80/40 responder rate fixed at 18.5%.

The results from sensitivity analyses are given in Appendix Table 4. The summary of results is listed below.

Case 1 results indicate that a change of 0.8% (18.5% to 17.7%), from the observed adalimumab 160/80/40 group rate of 18.5%, changes the 2-sided p-value (by Fisher's Exact test) from 0.0471 (less than 5%) to 0.0681 (greater 5%). T his difference of 0.8% is numerically equivalent to 1 responders in adalimumab 160/80/40 group in the numerator of the responder rate when given that the size of the adalimumab 160/80/40 group and placebo groups are 130.

Case 2 results indicate that a change of 0.8% (9.2% to 10.0%), from the observed placebo rate of 9.2%, changes the 2-sided p-value (by Fisher's Exact test) from 0.0471 (less than 5%) to 0.0748 (greater 5%). This difference of 0.8% is numerically equivalent to 1 responders in placebo in the numerator of the responder rate when given that the size of the adalimumab 160/80/40 group and placebo groups are 130.

Case 1 and Case 2 results indicate that alternations in the responder status of 1 subjects in the adalimumab 160/80/40 group (from responder to non- responder in the adalimumab 160/80/40 group) or 1 subject in the placebo group (i.e., from non-responder to responder in the placebo group) could change the observed 2-sided p-value <0.05 to greater than 0.05.

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This study could be a "negative" study, if a change in the responder status of 1 subjects in the adalimumab 160/80/40 group from responder to non-responder , or in the responder status of just 1 placebo subject from non-responder to responder.

3.1.1.3.5 Subgroup Analyses

Results of subgroup analyses of remission at Week 8 for subgroups: sex, age, race, weight, CRP, tobacco use, corticosteroid use at baseline, and Azathioprine or 6-MP use at baseline, are given below.

Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-826
(ITT-A3 Set-NRI)

Subgroup	Placebo Rate	Adalimumab 80/40 Rate	95% CI	Adalimumab 160/80/40 Rate	95% CI
Gender					
Male	7/82 (8.5%)	7/78 (9.0%)	(-8.3%, 9.2%)	13/83 (15.7%)	(-2.8%, 17.0%)
Female	5/48 (10.4%)	6/52 (11.5%)	(-11.1%, 13.4%)	11/47 (23.4%)	(-1.9%, 27.9%)
Age					
<40	9/72 (12.5%)	8/63 (12.7%)	(-11.0%, 11.4%)	16/74 (21.6%)	(-3.0%, 21.2%)
40-64	3/54 (5.6%)	4/59 (6.8%)	(-7.6%, 10.1%)	7/51 (13.7%)	(-3.1%, 19.4%)
≥65	0/4 (0.0%)	1/8 (12.5%)	(-10.4%, 35.4%)	1/5 (20.0%)	(-15.1%, 55.1%)
Race					
White	10/117 (8.5%)	12/119 (10.1%)	(-5.9%, 8.9%)	22/119 (18.5%)	(1.3%, 18.6%)
Non-white	2/13 (15.4%)	1/11 (9.1%)	(-32.2%, 19.7%)	2/11 (18.2%)	(-27.3%, 32.9%)
Weight					
< 70 kg	5/35 (14.3%)	6/40 (15.0%)	(-15.3%, 16.7%)	11/45 (24.4%)	(-6.9%, 27.2%)
≥70 kg	7/95 (7.4%)	7/90 (7.8%)	(-7.2%, 8.0%)	13/85 (15.3%)	(-1.4%, 17.2%)
CRP					
<10.0 mg/L	7/95 (7.4%)	9/87 (10.3%)	(-5.3%, 11.3%)	21/101 (20.8%)	(3.9%, 22.9%)
≥10.0 mg/L	4/32 (12.5%)	4/40 (10.0%)	(-17.3%, 12.3%)	2/25 (8.0%)	(-20.1%, 11.1%)
Smoker					
Ex-smoker	2/35 (5.7%)	4/46 (8.7%)	(-8.2%, 14.2%)	6/37 (16.2%)	(-3.6%, 24.7%)
Smoker	0/7 (0.0%)	1/8 (12.5%)	(-10.4%, 35.4%)	4/12 (33.3%)	(6.7%, 60.0%)
Non-smoker	10/88 (11.4%)	8/76 (10.5%)	(-10.4%, 8.7%)	14/81 (17.3%)	(-4.7%, 16.5%)
Corticosteroid Use at baseline					
Yes	8/89 (9.0%)	9/74 (12.2%)	(-6.4%, 12.7%)	12/71 (16.9%)	(-2.6%, 18.5%)
No	4/41 (9.8%)	4/56 (7.1%)	(-13.9%, 8.7%)	12/59 (20.3%)	(-3.1%, 24.3%)
Azathioprine and 6-Mercapto-purine therapy at baseline					
Yes	2/52 (3.8%)	6/51 (11.8%)	(-2.4%, 18.2%)	8/51 (15.7%)	(0.6%, 23.1%)
No	10/78 (12.8%)	7/78 (8.9%)	(-13.7%, 5.8%)	16/79 (20.3%)	(-4.1%, 19.0%)

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Complied from Tables 14.2_10.1 to 14.2_10.11.
95% CI based on normal approximation to the binomial distribution..

As seen from table above, 95% CIs for the difference in clinical remission at Week 8 between adlimumab 80/40 and placebo included zero for all subgroups.

95% CIs for the difference in clinical remission at Week 8 between adlimumab 160/80/40 and placebo included zero for gender, age, weight, and corticosteroid use at baseline subgroups. 95% CI excluded zero for white, CRP <10.0 mg/L, smoker, and Azathioprine or 6-MP use at baseline.

Furthermore, there was inconsistency in the difference in clinical remission at Week 8 between adlimumab 160/80/40 and placebo for CRP (<10.mg/L, ≥10 mg/L) subgroup (13.4% for CRP < 10 mgL vs. -4.5% for CRP ≥10.0 mg/L) (Breslow-Day, p=0.0839).

3.1.1.3.6 Post-Hoc Analysis of FDA defined Clinical Remission

In the pre-sBLA meeting dated November 23, 2010, the medical division recommends that the post hoc analysis utilize a definition of clinical remission as total Mayo score ≤2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability).

However, the sponsor failed to perform the statistical analysis for FDA definition of clinical remission in the submission.

This reviewer performed the post-hoc analysis for FDA definition of clinical remission at Week 8. The result from analysis of the proportion of subjects with FDA defined clinical remission at Week 8 is given below.

Number and Percentage of Subjects with FDA defined Clinical Remission per Mayo Score at Week 8
Study M06-826
(ITT-A3 Set-NRI)

Treatment	Rate	vs. placebo Difference	vs. placebo p-value	95% C. I
ADA 80/40	7/130 (5.4%)	0.8%	1.000	(-4.5%, 6.1%)
ADA 160/80/40	17/130 (13.1%)	8.5%	0.027	(1.6%, 15.3%)
Placebo	6/130 (4.6%)			

Compiled by this reviewer.
P-values obtained from Fisher's Exact test.
95% C.I. obtained from normal approximation by this reviewer.

As seen from table above, in the ITT-A3 set the FDA defined clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was higher than that in the placebo group; this difference was statistically significant. However, there was no

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statistically significant difference observed between the adalimumab 80/40 treatment group and the placebo group.

3.1.1.3.7 New FDA defined Clinical Remission

It was found that there were two patients (335086505 and 859362655) in the adalimumab 160/80/40 treatment group had Mayo score of 2, with endoscopy subscore=0, stool frequency subscore=2, rectal bleeding subscore=0, and physician's global assessment subscore=0 were considered as responders based on the FDA defined definition, but were considered as non-responders based pre-specified definition.

The new FDA defined definition for clinical remission should be as total Mayo score ≤ 2 with rectal bleeding subscore=0 (no bleeding), endoscopy subscore=0 (e.g., no friability) and no individual subscore > 1. It will allow stool frequency subscore=0 or 1 and physician's global assessment subscore=0 or 1. It will be more stringent than both pre-specified and FDA defined definitions.

This reviewer performed the post-hoc analysis for new FDA definition of clinical remission at Week 8. The result from analysis of the proportion of subjects with new FDA defined clinical remission at Week 8 is given below.

Number and Percentage of Subjects with New FDA defined Clinical Remission per Mayo Score at Week 8
Study M06-826
(ITT-A3 Set-NRI)

Treatment	Rate	vs. placebo Difference	vs. placebo p-value	95% C. I.
ADA 80/40	7/130 (5.4%)	0.8%	1.000	(-4.5%, 6.1%)
ADA 160/80/40	15/130 (11.5%)	6.9%	0.067	(0.4%, 13.5%)
Placebo	6/130 (4.6%)			

Compiled by this reviewer.
P-values obtained from Fisher's Exact test.
95% C.I. obtained from normal approximation by this reviewer.

As seen from table above, in the ITT-A3 set the new FDA defined clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was numerically higher than that in the placebo group; but, it failed achieved statistical significance.

There was no statistically significant difference observed between the adalimumab 80/40 treatment group and the placebo group.

Per this reviewer's request, the sponsor performed observed case, complete case, and multiple imputation analyses for the new FDA definition of clinical remission for this study.

The results from these analyses are given Appendix Table 5.

Reference ID: 3200370

As seen from Appendix Table 5, similar results were observed for observed case and complete case analyses. In the ITT-A3 set the new FDA defined clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was barely statistically significant higher than that in the placebo group (p=0.042, chi-square test). Bu, it would fail achieved statistical significance at nominal value of 0.05 if more conservative method (e.g., Fisher's Exact method) were used (p=0.066).

3.1.1.3.8 Meta Analysis of Primary Efficacy Endpoint for ITT-E Data

This reviewer performed a Meta analysis of primary efficacy endpoint comparing Adalimumab 160/80/40 vs. placebo for ITT-E data. The result provided 95% CI (1.5%, 12.5%) which excludes zero. It reconfirmed the finding from the primary analysis for ITT-A3 data.

3.1.2 Study M06-827

3.1.2.1 Study Design

This study was a multicenter, randomized, double-blind, placebo controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis

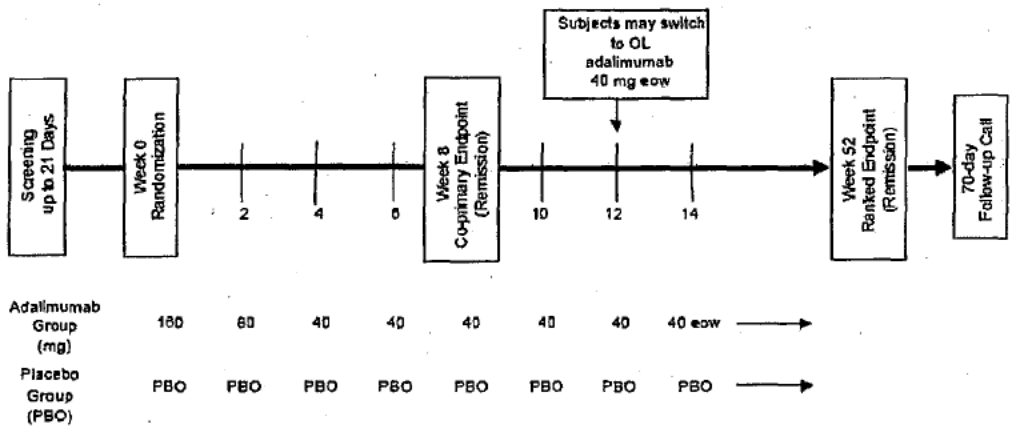
The primary objective of this study was to assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis (UC). The secondary objective of this study was to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration.

Adult subjects with moderate to severe UC (Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points), confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, were to be enrolled at approximately 120 sites worldwide.

Subjects were to be stratified by prior exposure to infliximab and/or other anti-TNF agents, and randomized in a 1:1 ratio to receive adalimumab or placebo by SC injection.

Reference ID: 3200370

Figure 1. Study Design Schematic



Subjects assigned to the adalimumab treatment arm were to receive an induction dose of 160 mg at Week 0 and 80 mg at Week 2, and 40 mg every other week (eow) starting at Week 4. Subjects assigned to the placebo treatment arm were to receive matching placebo during the same period of time.

At or after Week 10, subjects who met the criteria for inadequate response could have been switched to open-label (OL) adalimumab 40 mg eow beginning at Week 12. Inadequate response was defined as:

- Partial Mayo score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 4 to 7 at Baseline).
- Partial Mayo score ≥ 7 on 2 consecutive visits at least 14 days apart (for subjects with a Partial Mayo score of 8 or 9 at Baseline).

Subjects who demonstrated inadequate response at 2 consecutive visits at least 14 days apart while on OL adalimumab 40 mg eow were permitted to dose escalate to adalimumab 40 mg weekly (ew).

Subjects with persistent inadequate response while on adalimumab 40 mg ew may have been discontinued from the study at the Investigator's discretion. Upon completion of the study, subjects had the option to enroll into OLE Study M10-223 in which they could receive adalimumab treatment.

Enrollment was planned for 500 subjects. A total of 494 subjects comprised the ITT analysis set used for primary efficacy analyses; 24 subjects (14 randomized to adalimumab and 10 to placebo) from 3 sites (Sites 22635, 36809, and 27010) were excluded from the ITT analysis due to site noncompliance. A total of 517 subjects (including subjects at non-compliant sites) were analyzed as part of the Safety analysis set (518 subjects were randomized into the study, 1 subject did not receive study drug).

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Subjects at least 18 years of age with moderately to severely active UC (Mayo score of 6 to 12 points and an endoscopy subscore of 2 to 3 points, despite concurrent treatment with corticosteroids and/or immunosuppressants) confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy.

The duration of the study was up to 65 weeks, including a Screening Period of up to 3 weeks, a double-blind (DB), placebo-controlled treatment period of up to 52 weeks, and a 70 day follow-up phone call for subjects who prematurely discontinued or who did not enroll in the extension study (Study M10 223).

The Mayo score is a composite of the following subscore components: stool frequency subscore (SFS), RBS, endoscopy subscore, and PGA subscore .

All subjects were to be provided with a subject diary at the Screening Visit to record UC-related symptoms. The subject diary was to provide information on the subject-reported subscores for calculating the Mayo and partial Mayo score at each visit beginning at Baseline. The worst severity diary entry from the 3 days prior to each study visit was to be used for each subject-reported subscore. The Investigator was to use the subject – reported subscores of abdominal discomfort and functional assessment to determine the PGA subscore.

The Mayo score (consisting of the partial Mayo score plus the endoscopy subscore) was to be calculated at visits when an endoscopy was performed (i.e., Weeks 0, 8, 32, and 52/Early Termination Visits). The endoscopy score from the Screening endoscopy was to be used in the calculation of the Mayo score at Week 0 (Baseline). This score ranges from 0 to 12 points.

As defined in the protocol, the following definitions were to be used to describe the primary and secondary variables:

Clinical remission per Mayo score	Total Mayo score ≤ 2 and no individual subscore > 1.
Clinical response per Mayo Score	• Decrease in Mayo score of ≥ 3 points from Baseline AND • Decrease in Mayo score of $\geq 30\%$ from Baseline AND • Decrease in the rectal bleeding score (RBS) ≥ 1 or an absolute RBS of 0 or 1
Clinical response per partial Mayo score	• Decrease in partial Mayo score of ≥ 2 points from baseline AND • Decrease in partial Mayo score of $\geq 30\%$ from Baseline AND • Decrease in the RBS ≥ 1 from Baseline
ITT Analysis Set	All subjects with confirmed ulcerative colitis (UC) at Baseline who were randomized, and excluded subjects

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	from Dr. Wild's, Dr. Roeder's, and Dr. Kellner's sites.
Modified ITT Analysis Set	All subjects from the ITT analysis set who received at least 1 dose of study drug or placebo (N = 493). Exploratory efficacy analyses were performed on the modified ITT (mITT) analysis set.
Per Protocol Analysis Set	All subjects in the ITT analysis set after excluding subjects with major protocol deviations.
Safety Analysis Set	All subjects who received at least 1 dose of study drug (including those enrolled at Dr. Wild's, Dr. Roeder's, and Dr. Kellner's sites).
Mayo score	Composite score of UC disease activity based on total of subscores: • Endoscopy (0 – 3) • Stool frequency (0 – 3) • Rectal bleeding (0 – 3) • Physician's global assessment (PGA) (0 – 3)
Mucosal healing	Endoscopy subscore of 0 or 1
Complete mucosal healing	Endoscopy subscore of 0

The ranked co-primary efficacy endpoints were:
- The proportion of subjects who achieved remission at Week 8 and
- The proportion of subjects who achieved remission at Week 52.

Ranked secondary efficacy variables as described in the protocol were as follows:
- Proportion of subjects with remission (sustained) per Mayo score at both Weeks 8 and 52.
- Proportion of subjects who achieved response per Mayo score at Week 8; at Week 52 (No. 3); at both Weeks 8 and 52 (No. 4).
- Proportion of subjects who achieved mucosal healing at Week 8; at Week 52 (No. 6); at Both Weeks 8 and 52 (No. 7).
- Proportion of subjects who discontinued corticosteroid use before Week 52 and achieved remission at Week 52.
- Proportion of subjects with PGA subscore indicative of mild disease (≤ 1) at Week 8.
- Proportion of subjects with stool frequency subscore (SFS) indicative of mild disease (≤ 1) at Week 8.
- Proportion of subjects with rectal bleeding subscore (RBS) indicative of mild disease (≤ 1) at Week 8.
- Proportion of subjects who discontinued corticosteroid use for at least 90 days before Week 52 and achieved remission at Week 52.
- Proportion of subjects who discontinued corticosteroid use and achieved remission at both Weeks 32 and 52.
- Proportion of subjects who were inflammatory bowel disease questionnaire (IBDQ) responders at Week 52; and at Week 8 (No. 15).

Non-ranked secondary variables as described in the protocol were as follows:
- Proportion of subjects who achieved remission at Week 32 and (sustained) throughout

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Weeks 8, 32, and 52.

- Proportion of subjects who achieved response per Mayo score at Week 32 and throughout Weeks 8, 32, and 52.
- Proportion of subjects who achieved response per partial Mayo score at each time point separately.
- Time to response per partial Mayo score.
- Duration of response per partial Mayo score.
- Proportion of subjects who discontinued corticosteroid use for ≥ 90 days and achieved remission at Week 32.
- Proportion of subjects who discontinued corticosteroid use and achieved remission at Week 32.
- Proportion of subjects who have discontinued corticosteroid use at each time point after Week 8 separately.
- Duration of steroid-free response per partial Mayo score for subjects who were using corticosteroids at Baseline.
- Proportion of subjects who were IBDQ responders at Week 32, at both Weeks 8 and 52, and throughout Weeks 8, 32 and 52.
- Proportion of subjects with IBDQ score ≥ 170 at each time point separately.
- Change from Baseline in IBDQ score, SF-36 score, Mayo score, endoscopy score, SFS, RBS, and PGA subscore at each time point separately.
- Proportion of subjects who achieved mucosal healing at each time point separately.
- Proportion of subjects with RBS indicative of mild disease (≤ 1) at each time point separately.
- Time in minimal rectal bleeding (RBS ≤ 1).
- Proportion of subjects with PGA subscore indicative of mild disease (≤ 1) at each time point separately.
- Proportion of subjects with SFS indicative of mild disease (≤ 1) at each time point separately.
- Proportion of subjects requiring dose escalation to 40 mg ew.
- Proportion of subjects achieving response (per Mayo score and per partial Mayo score) at Week 52 after dose escalation.
- Proportion of subjects achieving remission at Week 52 after dose escalation for a) subjects who had not achieved response per partial Mayo score prior to dose escalation and b) subjects who had achieved response per partial Mayo score but lost response (had inadequate response) prior to dose escalation.
- Change from Baseline in WPAI at each time point separately.
- Health care resource utilization at each time point separately.
- Colectomy rates during the study.

The sample size was calculated using nQuery Advisory 4.0. Assuming that 5% of the subjects in the placebo group achieved clinical remission at Week 52 or Week 8, a sample size of 250 in each treatment group was adequate to detect a difference of at least 7 percentage points from the adalimumab group using Chi-square test with 80% power at a 0.05 two-sided significance level. Thus, a total of 500 subjects were to be randomized in this study.

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3.1.2.2 Sponsor's Analysis

A total of 518 subjects were randomized into the study at 103 sites in the US, Canada, Austria, Belgium, Denmark, France, Germany, Israel, Norway, Portugal, Spain, Switzerland, the Czech Republic, Hungary, Poland, Australia, and New Zealand. The number of subjects per site ranged from 1 to 22. One subject randomized to adalimumab did not receive study drug. Of the 518 subjects who entered the study, 24 subjects (14 randomized to adalimumab and 10 to placebo) from 3 sites (Dr. Wild's [22635], Dr. Roeder's [36809], and Dr. Kellner's [27010] sites) were excluded from the ITT analysis due to site noncompliance.

Disposition of subjects is presented below for the ITT analysis.

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Disposition of Subjects (ITT Population)
Study M06-827

Subject Status – All randomized	Number (%) of Subjects		
	Placebo	Adalimumab	Total
Randomized	260	258	518
Treated	260	257	517
Subject Status – Final (ITT Analysis Set)	**Placebo N = 246**	**Adalimumab N = 248**	**Total N = 494**
Discontinued study	115 (46.7)	94 (37.9)	209 (42.3)
Reasons for discontinuation[a]			
Adverse event	25 (10.2)	12 (4.8)	37 (7.5)
Withdrew consent	4 (1.6)	8 (3.2)	12 (2.4)
Lost to follow-up	0	1 (0.4)	1 (0.2)
Lack of efficacy	70 (28.5)	63 (25.4)	133 (26.9)
Protocol violation	5 (2.0)	1 (0.4)	6 (1.2)
Other[b]	11 (4.5)	9 (3.6)	20 (4.0)
Subject Status – Week 8 (ITT Analysis Set)			
Discontinued study prior to Week 8	36 (14.6)	23 (9.3)	59 (11.9)
Reasons for discontinuation[a]			
Adverse event	10 (4.1)	5 (2.0)	15 (3.0)
Withdrew consent	2 (0.8)	1 (0.4)	3 (0.6)
Lost to follow-up	0	0	0
Lack of efficacy	15 (6.1)	13 (5.2)	28 (5.7)
Protocol violation	3 (1.2)	1 (0.4)	4 (0.8)
Other[b]	6 (2.4)	3 (1.2)	9 (1.8)

a. Primary reason.

b. Reasons for discontinuation recorded as "other" included: diagnosis of CD, loss of response, primary nonresponder, UC symptoms not improving, investigator decision, subject noncompliance, positive TB skin test, subject wanted to start family, or total colectomy surgery within the 70-day follow-up period.

Cross reference: Table 14.1__1.1, Table 14.1__2.1.1.1, and Table 14.1__2.1.3.1.1

As seen table above, a total of 11.9% of subjects in the ITT analysis set discontinued prior to Week 8, most frequently due to lack of efficacy, which occurred at a higher incidence rate in the placebo group compared to the adalimumab group. By the end of the study (Week 52), a total of 42.3% of subjects discontinued prematurely. The most frequently reported reasons for premature discontinuation were lack of efficacy, AE, and other, all of which were experienced in a numerically greater proportion of subjects randomized to the placebo group. All other reasons for discontinuation were each reported by < 3.5% of subjects.

At or after Week 10, subjects who met the criteria for inadequate clinical response could have been switched to OL adalimumab 40 mg eow beginning at Week 12.
In the ITT analysis set, a total of 251 subjects switched to OL administration (135 who

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had been randomized to placebo and 116 who had been randomized to adalimumab). Subjects who demonstrated inadequate clinical response at 2 consecutive visits at least 14 days apart while on OL adalimumab 40 mg eow were permitted to dose escalate to adalimumab 40 mg ew. A total of 152 subjects dose-escalated from eow to ew adalimumab (84 who had been randomized to placebo and 68 who had been randomized to adalimumab).

Major protocol deviations were defined according to ICH as received wrong treatment or incorrect dose of study drug, inclusion and/or exclusion criteria violation, use of prohibited concomitant medication, and development of withdrawal criteria without being withdrawn.

A summary of protocol deviation in the ITT analysis set is given below.

Protocol Deviations (ITT Analysis Set)
Study M06-827

	Number (%) of Subjects		
Deviation Category	Placebo N = 246	Adalimumab N = 248	Total N = 494
Inclusion/Exclusion Criteria Violation	32 (13.0)	40 (16.1)	72 (14.6)
Developed Withdrawal Criteria/Was Not Withdrawn	0	0	0
Received Wrong Treatment or Incorrect Dose	26 (10.6)	31 (12.5)	57 (11.5)
Received Excluded Concomitant Treatment	55 (22.4)	45 (18.1)	100 (20.2)

Cross reference: Table 14.1__2.2.2

As seen from table above, the most common protocol deviation was use of excluded concomitant treatment, which occurred in a greater proportion of subjects in the placebo group than in the adalimumab group.

Inclusion/exclusion criteria protocol deviations occurred in 14.6% of subjects. Inclusion Criterion No. 3, the requirement that subjects be diagnosed with active UC confirmed by colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, was the most frequently violated inclusion/exclusion criteria (6.7%), and occurred in similar proportions of subjects in both treatment groups.

A total of 11.5% of subjects received incorrect treatment or dose with similar proportions in each treatment group.

Four analysis sets were used in the analysis of study data. A summary of analysis sets is given below.

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Analysis Sets
Study M06-827

Analysis Set	Number (%) of Subjects		
	Placebo N = 260	Adalimumab N = 258	Total N = 518
Safety	260	257[a]	517
Intent-to-Treat	246	248	494
Modified Intent-to-Treat	246	247	493
Per Protocol	212	212	424

a. One subject was randomized to adalimumab but never treated.

Note: A total of 24 subjects were excluded from the ITT and mITT analysis set due to non-compliance with GCP and protocol requirements at the investigative sites (Sites 22635, 36809, and 27010).

Cross reference: Table 14.1__1.1

3.1.2.2.1 Planned Analysis

The primary efficacy analysis was performed on the ITT analysis set and consisted of two ranked efficacy endpoints: (1) proportion of subjects achieving clinical remission at Week 8 and (2) proportion of subjects achieving clinical remission at Week 52. Hypothesis testing for the ranked endpoints was carried out in a hierarchical order using a two-sided Cochran Mantel Haenszel (CMH) test adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 8 was tested first. If the null hypothesis of no difference between adalimumab and placebo in remission rate at Week 8 was rejected at $\alpha = 0.05$, then the remission rate at Week 52 was to be tested at a significance level of 0.05.

However, in order to claim maintenance of remission, it was necessary to reject not only both hypotheses on the two ranked co-primary endpoints but also to reject the hypothesis on the first ranked secondary endpoint (proportion of subjects in remission at both Week 8 and Week 52). This first ranked secondary endpoint was incorporated in the confirmatory testing procedure conducted in hierarchical order from the first to the second ranked co-primary efficacy endpoint, and then to the ranked secondary endpoints, and stopped whenever a hypothesis could not be rejected at a significance level of 0.05. If a ranked endpoint did not meet the criteria for statistical significance, the analyses of the rest of the ranked secondary endpoints would be considered exploratory. This ensured that the multiple significance level was controlled at 0.05.

Non-responder imputation was used in the analysis. Subjects who discontinued the study for any reason and subjects with a missing Mayo Score were counted as non-remitters. Subjects who switched to OL drug were counted as non-remitters from the time of switching onward.

The last observation carried forward (LOCF) method was used for sensitivity analyses. For subjects who switched to OL drug, the non-missing value at the visit when the subject switched to the OL drug was to be carried forward in the LOCF analysis.

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The secondary efficacy analysis was performed on the ITT analysis set. The testing of ranked secondary endpoints was initiated only in case of statistically significant differences between the treatment groups for both ranked co-primary endpoints. The statistical tests for the ranked secondary variables were carried out in hierarchical order.

The difference in proportions of subjects between treatment groups was analyzed using the Cochran-Mantel-Haenszel test adjusted for prior exposure to infliximab or other anti-TNF agents.

Non-responder imputation was used in the analysis of the ranked dichotomous secondary variables. LOCF was used as a sensitivity analysis.

Non-ranked categorical secondary efficacy variables were analyzed by non-responder imputation and by LOCF as a sensitivity analysis using the CMH test. Change from Baseline in Mayo Score, IBDQ, SF-36, and WPAI were analyzed using an ANCOVA model including factors of treatment, prior exposure to infliximab or other anti-TNF agents, and Baseline values. For changes, both LOCF and as observed cases were used as imputation methods. Duration of response and time to response data were analyzed using Kaplan-Meier curves and a proportional hazards model, including treatment factors and prior exposure to infliximab or other anti-TNF agents.

3.1.2.2.2 Treatment Group Comparability

The summary of results of comparability of treatment groups at baseline for ITT-A3 are given in Appendix Tables 5 to 7 respectively for demographic characteristics, baseline disease history, baseline disease activity, and baseline disease severity by Mayo subscore.

As seen from Appendix Tables 6 to 8, the majority of subjects were male, white, and < 40 years old. There were no statistically significant differences observed between the treatment groups.

Among the Baseline outcomes questionnaires, the adalimumab treatment group had a statistically significantly higher SF-36 mental component summary score, role-emotional functioning component score, and mental health component score compared with placebo ($P = 0.012$, 0.004, and 0.037, respectively). There were no other statistically significant differences observed between treatment groups.

Baseline disease characteristics found for this study are consistent with the UC population of interest.

The majority of subjects in both treatment groups had moderate to severe disease at Baseline as assessed by endoscopy, rectal bleeding, PGA, and SFS. Subscores were very similar between groups and no statistically significant differences were found.

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3.1.2.2.3 Sponsor's Analysis of Primary Efficacy Parameter

The ranked co-primary efficacy endpoints were:
- The proportion of subjects who achieved remission at Week 8 and
- The proportion of subjects who achieved remission at Week 52.

Remission per Mayo score was defined as Mayo score (composite score based on SFS, RBS, PGA, and endoscopy) ≤ 2 with no subscore > 1.

Hypothesis testing for the ranked co-primary endpoints was carried out in a hierarchical order using a two-sided CMH test adjusted for prior exposure to infliximab or other anti-TNF agents. The remission rate at Week 8 was tested first. If the null hypothesis of no difference between adalimumab and placebo in remission rates at Week 8 was rejected at a significance level of 0.05, then the remission rate at Week 52 was tested at a significance level of 0.05.

Number of Subjects with Remission per Mayo Score at Week 8 and Week 52
Study M06-827
(ITT Set- NRI)

	Treatment	vs. Placebo Rate	vs. Placebo Difference	p-value	95% C.I.
Week 8	Adalimumab	41/248 (16.5%)	7.2%	0.019	(1.3%, 13.1%)
	Placebo	23/246 (9.3%)			
Week 52	Adalimumab	43/248 (17.3%)	8.8%	0.004	(2.9%, 14.7%)
	Placebo	21/246 (8.5%)			

Compiled from Table 20.
P-values obtained from CMH test (stratification levels: prior anti-TNF versus anti-TNF-naïve).
95% C.I. obtained from normal approximation by this reviewer.

As seen from table above, a statistically significantly greater proportion of subjects in the adalimumab group were in clinical remission per Mayo score at Week 8 and Week 52 compared to subjects in the placebo group in ITT set.

3.1.2.2.3.1 Sensitivity Analyses

The sponsor also performed sensitivity analyses for primary efficacy endpoint. Sensitivity analyses included mITT -NRI, LOCF and Per Protocol-NRI analyses. In the LOCF analysis, the last non-missing post-baseline values were carried forward.

The results from sensitivity analyses are given below.

Reference ID: 3200370

Sensitivity Analyses
Study M06-827
(ITT- Set)

Endpoint	Analysis	Placebo Rate	Adalimumab Rate	Diff (Ada-Pla)	p-value[a]
Week 8	mITT - NRI	23/246 (9.3%)	41/247 (16.6%)	7.3%	0.018
	Per Protocol-NRI	21/212 (9.9%)	36/212 (17.0%)	7.1%	0.027
	ITT – LOCF	23/217 (10.6%)	41/225 (18.2%)	7.6%	0.024
Week 52	mITT - NRI	21/246 (8.5%)	43/247 (17.4%)	8.9%	0.004
	Per Protocol-NRI	19/212 (9.0%)	35/212 (16.5%)	7.5%	0.015
	ITT – LOCF	23/219 (10.5%)	46/231 (19.9%)	9.4%	0.006

Complied from Table 35
[a]p-values obtained from Chi-square test.

As seen from table above, similar results were seen in the mITT – NRI, PP-NRI analysis and the ITT set when LOCF imputation was used instead of NRI imputation.

3.1.2.2.4 Sponsor's Analyses of Secondary Variables

Fifteen ranked secondary variables were tested in a hierarchical order, and testing was only allowed to be started if the ranked co-primary endpoints were significant. Statistically significant results ($P \leq 0.05$) had to be achieved for a comparison in the higher rank to initiate the next comparison in the lower rank.

Summary of results of ranked secondary endpoint for ITT-NRI is given below.

Reference ID: 3200370

Summary of Results of Ranked Secondary Endpoints
Study M06-827
(ITT Analysis Set: NRI)

Ranked Secondary Endpoints:[a]	Number (%) of Subjects		
	Placebo N = 246	Adalimumab N = 248	*P* value
1. Sustained remission per Mayo score at Week 8 and Week 52	10 (4.1)	21 (8.5)	0.047
2. Response per Mayo score at Week 8	85 (34.6)	125 (50.4)	< 0.001
3. Response per Mayo score at Week 52	45 (18.3)	75 (30.2)	0.002
4. Sustained Response per Mayo score at Week 8 and Week 52	30 (12.2)	59 (23.8)	< 0.001
5. Mucosal healing at Week 8	78 (31.7)	102 (41.1)	0.032
6. Mucosal healing at Week 52	38 (15.4)	62 (25.0)	0.009
7. Sustained mucosal healing at Week 8 and Week 52	26 (10.6)	46 (18.5)	0.013
8. Discontinued corticosteroid use before Week 52 and achieved remission at Week 52	8 (5.7)	20 (13.3)	0.035
9. PGA ≤ 1 at Week 8	92 (37.4)	114 (46.0)	0.058
10. SFS ≤ 1 at Week 8	70 (28.5)	94 (37.9)	0.028
11. RBS ≤ 1 at Week 8	143 (58.1)	174 (70.2)	0.006
12. Discontinued corticosteroid use for ≥ 90 days before Week 52 and achieved remission at Week 52	8 (5.7)	20 (13.3)	0.035
13. Discontinued corticosteroid use and achieved sustained remission at both Weeks 32 and 52	2 (1.4)	15 (10.0)	0.002
14. IBDQ responders at Week 52	40 (16.3)	65 (26.2)	0.007
15. IBDQ responders at Week 8	112 (45.5)	144 (58.1)	0.006

IBDQ = Inflammatory Bowel Disease Questionnaire; PGA = physician's global assessment subscore; RBS = rectal bleeding subscore; SFS = stool frequency subscore

a. Listed in ranked order, as indicated by the number preceding each endpoint variable.

Cross reference: Tables 14.2__3.1 through 14.2__17.1

As seen from table above, the first 8 ranked endpoints met the criteria for statistical significance these endpoints included sustained clinical remission per Mayo score at both Weeks 8 and 52, clinical response per Mayo score at Week 8 and at Week 52, sustained clinical response per Mayo score at both Weeks 8 and 52, mucosal healing (defined as endoscopy subscore ≤ 1) at Week 8 and at Week 52, sustained mucosal healing at both Weeks 8 and 52, and (among subjects using corticosteroids at Baseline) steroid-free clinical remission per Mayo score at Week 52. Ranked endpoint No. 9 (PGA ≤ 1 at Week 8 in the adalimumab treatment group versus placebo) narrowly missed statistical significance (p = 0.058), although it exhibited a numerical benefit of the adalimumab treatment group versus placebo.

The adalimumab treatment group had a statistically significantly greater proportion of subjects meeting the rest of the ranked endpoints (*P* value ranged from 0.002 to 0.035) compared with placebo.

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3.1.2.3 Reviewer's Comments and Evaluation

3.1.2.3.1 Study Design

This study was designed for induction of clinical remission and induction of sustained clinical remission in subjects with moderately to severely active ulcerative colitis. This study was not designed for maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis.

Rejecting not only both hypotheses on the two co-primary endpoints (proportion of subjects who achieve remission at Week 8 and proportion of subjects who achieve remission at Week 52) by hierarchical order but also the hypothesis on the first ordered secondary endpoint (proportion of subjects in remission at both Week 8 and Week 52) would only show that sustained remission at both Week 8 and Week 52.

For a claim for maintenance of remission, the study design should be designed as a maintenance trial or a maintenance phase should be added after the induction phase.

In this study, subjects who had disease flare or non-response were allowed to switch to open-label (OB) adlimumab treatment after Week 12. Given the option of OL escape, the number of subjects who remained on DB treatment through Week 52 was relative small.

With more than 70% of subjects with missing data at both Week 8 and Week 52, the treatment group difference in sustained remission rate at Week 8 and Week 52 would not be reliable.

3.1.2.3.2 Sensitivity Analyses for Primary Efficacy Endpoints

Per this reviewer's request, the sponsor had performed observed case, complete case, and multiple imputation analyses.

The results from sensitivity analyses are given below.

Sensitivity Analyses
Study M06-827
(ITT- Set)

Endpoint	Analysis	Placebo Rate	Adalimumab Rate	Diff (Ada-Pla)	p-value[a]
Week 8	Observed Case	23/213 (10.8%)	41/220 (18.6%)	7.8%	0.023
	Completed Case	12/54 (22.2%)	28/79 (35.4%)	13.2%	0.101
	Multiple Imputation	9.7%	17.3%	7.6%	0.017
Week 52	Observed Case	21/58 (36.2%)	43/82 (52.4%)	16.2%	0.059
	Completed Case	21/56 (37.5%)	43/82 (52.4)	14.9%	0.083
	Multiple Imputation	25.5%	37.0%	11.5%	0.034

Complied from Tables 2_1.1, 2_1.2, 2_2.1, 2_2.2, 2_3.1, and 2__3.2.
[a]p-values obtained from CMH with stratification: prior anti-TNF vs. prior anti-TNF naïve.

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As seen from table above, similar results were seen in the observed case, complete case, and multiple imputation analyses for remission rate at Week 8. For remission rate at Week 52, only multiple imputation analysis achieved statistical significance.
There was disproportional missing at week 52 against placebo (202/280 vs. 176/258, p=0.0152). With more than 70% missing at Week 52, the results from remission rate at week 52 might not be reliable and trustworthy.

3.1.2.3.3 Reviewer's Comments on Sponsor's Analysis of Sustained Remission per Mayo Score at Week 8 and Week 52

There was disproportionate missing data for subjects for sustained remission per Mayo score at week 8 and week 52. More placebo subjects had missing data for sustained remission per Mayo score at week 8 and week 52 as compared to adalimumab (204/260 vs. 169/258, p=0.0010). With more than 70% missing at Week 8 and Week 52, the results from sustained remission rate at week 8 and week 52 might not be reliable and trustworthy.

Therefore the sponsor's ITT analysis with NRI imputation tends to be biased in favor of adalimumab.

Furthermore, the sponsor's result might be method dependent. It would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.0621).

Per this reviewer's request, the sponsor had performed observed case, complete case, and multiple imputation analyses.

The results from sensitivity analyses are given below.

Sensitivity Analyses
Study M06-827
(ITT- Set)

Endpoint	Analysis	Placebo Rate	Adalimumab Rate	Diff (Ada-Pla)	p-value[a]
Week 8 &	Observed Case	10/56 (17.9%)	21/79 (26.6%)	8.7%	0.231
Week 52	Completed Case	10/54 (18.5%)	21/79 (26.6%)	8.1%	0.271
	Multiple Imputation	6.3%	12.1%	5.8%	0.034

Complied from Tables 2_1.3, 2_2.3, and 2_3.3.
[a]p-values obtained from CMH with stratification: prior anti-TNF vs. prior anti-TNF naïve.

As seen from table above, both observed case and completed cases analyses failed to achieve statistical significance due to small sample size.

Therefore, the results from analysis of sustained remission per Mayo score at week 8 and week 52 might not be robust.

Reference ID: 3200370

3.1.2.3.4 Reviewer's Comments on Sponsor's Analyses of Secondary Variables

Fifteen ranked secondary variables were tested in a hierarchical order, and testing was only allowed to be started if the ranked co-primary endpoints were significant. Statistically significant results ($p \leq 0.05$) had to be achieved for a comparison in the higher rank to initiate the next comparison in the lower rank.

For the first ranked endpoints, sustained remission per Mayo score at Week 8 and Week 52, the result of sponsor's analysis was closed to 0.05. As stated in previous section, it was found that the sponsor's result might be method dependent, biased in favor of adalimumab, and might not be robust.

So, lower ranked variable should not be initiated, according to hierarchical testing procedure to control the type I error. Analyses for all secondary variable should be considered as exploratory.

3.1.2.3.5 Subgroup Analyses

Results of subgroup analyses of co-primary endpoints (remission at Week 8 and remission at Week 52)) for subgroups: sex, age, race, weight, CRP, tobacco use, corticosteroid use at baseline, and Azathioprine or 6-MP use at baseline are given below.

Reference ID: 3200370

Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 8		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	(0.1%, 15.2%)
Female	10/94 (10.6%)	18/106 (17.0%)	(-3.1%, 15.8%)
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	(2.4%, 17.9%)
40-64	13/116 (11.2%)	17/105 (16.2%)	(-4.1%, 14.1%)
≥65	2/12 (16.7%)	1/7 (14.3%)	(-33.8%, 31.0%)
Race			
White	23/234 (9.8%)	38/236 (16.1%)	(0.2%, 12.3%)
Non-white	0/12 (0.0%)	3/12 (25.0%)	
Weight			
< 70 kg	7/91 (7.7%)	16/95 (16.8%)	(-0.2%, 18.5%)
≥70 kg	16/155 (10.3%)	25/153 (16.3%)	(-1.7%, 13.3%)
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	(2.0%, 18.6%)
Yes	7/101 (6.9%)	9/98 (9.2%)	(-5.3%, 9.8%)
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	(0.0%, 15.2%)
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	(-3.0%, 13.1%)
Smoker			
Ex-smoker	7/88 (8.0%)	15/94 (16.0%)	(-1.3%, 17.3%)
Smoker	2/19 (10.5%)	2/20 (10.0%)	(-19.5%, 18.5%)
Non-smoker	14/138 (10.1%)	24/134 (17.9%)	(-0.5%, 16.0%)
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	(-12.4%, 8.3%)
No	11/166 (6.6%)	29/155 (18.7%)	(4.9%, 19.3%)
Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	(3.3%, 19.5%)
No	10/106 (9.4%)	10/98 (10.2%)	(-7.4%, 8.9%)

Complied from Tables 14.2_61.1.1 to 14.2_61.18, 14.2_62.1.1 – 14.2_62.1.18.
95% CI based on normal approximation to the binomial distribution..

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Number and Percentage of Subjects with Remission per Mayo Score at Week 52 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 52		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Gender			
Male	18/152 (11.8%)	23/142 (16.2%)	(-3.6%, 12.3%)
Female	3/94 (3.2%)	20/106 (18.9%)	(7.4%, 23.9%)
Age			
<40	11/118 (9.3%)	27/136 (19.9%)	(2.0%, 19.0%)
40-64	9/116 (7.8%)	16/105 (15.2%)	(-0.9%, 15.9%)
≥65	1/12 (8.3%)	0/7 (0.0%)	(-24.0%, 7.3%)
Race			
White	21/234 (9.0%)	38/236 (16.1%)	(1.2%, 13.1%)
Non-white	0/12 (0.0%)	5/12 (41.7%)	(13.8%, 70.0%)
Weight			
< 70 kg	5/91 (5.5%)	20/95 (21.1%)	(6.1%, 25.0%)
≥70 kg	16/155 (10.3%)	23/153 (15.0%)	(-2.7%, 12.1%)
Prior Anti-TNF Treatment			
No	18/145 (12.4%)	33/150 (22.0%)	(1.1%, 18.1%)
Yes	3/101 (3.0%)	10/98 (10.2%)	(0.4%, 14.1%)
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	(1.4%, 16.2%)
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	(-8.4%, 16.9%)
Smoker			
Ex-smoker	9/88 (10.2%)	12/94 (12.8%)	(-6.7%, 11.8%)
Smoker	0/19 (0.0%)	5/20 (25.0%)	(6.0%, 44.0%)
Non-smoker	12/138 (8.7%)	26/134 (19.4%)	(2.5%, 18.9%)
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	8/80 (10.0%)	17/93 (18.3%)	(-2.0%, 18.5%)
No	13/166 (7.8%)	26/155 (16.8%)	(1.8%, 16.1%)
Corticosteroid Use at baseline			
Yes	10/140 (7.1%)	25/150 (16.7%)	(2.2%, 16.9%)
No	11/106 (10.4%)	18/98 (18.4%)	(-1.6%, 17.6%)

Complied from Tables 14.2_61.1.1 to 14.2_61.18, 14.2_62.1.1 – 14.2_62.1.18.
95% CI based on normal approximation to the binomial distribution..

Reference ID: 3200370

As seen from table above, 95% CIs for the difference in clinical remission at Week 8 between adlimumab and placebo included zero for subgroups of weight and smoker.

95% CIs for the difference in clinical remission at Week 8 between adlimumab and placebo excluded zero for male, age < 40, white, no prior Anti-TNF treatment, CRP <10.0 mg/L,and corticosteroid use at baseline.

Furthermore, there was inconsistency in the difference in clinical remission at Week 8 between adlimumab and placebo for Azathioprine or 6-MP use at baseline (yes vs. no) subgroup (-2.1% for yes vs. 12.1% for no) (Breslow-Day, p=0.0175).

95% CIs for the difference in clinical remission at Week 52 between adlimumab and placebo excluded zero for female, age < 40, white and non-white, weight < 70 kg, no prior Anti-TNF treatment, CRP <10.0 mg/L, smoker and non-smoker, and corticosteroid use at baseline.

3.1.2.3.6 Post-Hoc Analysis of FDA defined Remission

In the pre-sBLA meeting dated November 23, 2010, the medical division recommends that the post hoc analysis utilize a definition of Clinical Remission as total Mayo score ≤2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability).

The new FDA defined definition for clinical remission is total Mayo score ≤2 with rectal bleeding subscore=0 (no bleeding), endoscopy subscore=0 (e.g., no friability) and no individual subscore > 1.

However, the sponsor failed to perform the statistical analysis for new FDA definition of clinical remission in the submission.

This reviewer performed the post-hoc analyses for new FDA definition of clinical remission at Week 8, Week 52, and Week 8 and Week 52. The result from analyses of the proportion of subjects with FDA defined clinical remission at Week 8, Week 52, and Week 8 and Week 52 are given below.

Number of Subjects with New FDA definition of Clinical Remission per Mayo Score at Week 8, Week 52 and Week 8 and Week 52
Study M06-827
(ITT Set- NRI)

	Treatment	vs. Placebo Rate	vs. Placebo Difference	p-value	95% C. I.
Week 8	Adalimumab	23/248 (9.3%)	5.2%	0.029	(0.8%, 9.6%)
	Placebo	10/246 (4.1%)			
Week 52	Adalimumab	31/248 (12.5%)	7.6%	0.004	(2.7%, 12.5%)
	Placebo	12/246 (4.9%)			

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Week 8 & Week 52	Adalimumab	10/248 (4.0%)	2.8%	0.088	(0.0%, 5.6%)
	Placebo	3/246 (1.2%)			

Compiled by this reviewer.
P-values obtained from Fisher's Exact test.
95% C.I. obtained from normal approximation by this reviewer.

As seen from table above, for the new FDA definition of clinical remission, the treatment difference achieved statistical significance at nominal significance level of 0.05 at Week 8 and at Week 52. But, it failed to achieve significance at nominal p-value 0.05 at Week 8 and Week 52.

Per this reviewer's request, the sponsor performed observed case, complete case, and multiple imputation analyses for the new FDA definition of clinical remission for this study.

The results from these analyses are given Appendix Table 9

As seen from Appendix Table 9, for the new FDA defined clinical remission, in ITT data set, the treatment difference for the new FDA defined clinical remission, the treatment difference achieved statistical significance at nominal significance level of 0.05 at Week 8. It achieved barely statistical significance at nominal significance level of 0.05 at Week 52. But, it failed to achieve significance at nominal p-value 0.05 at both Week 8 and Week 52.

3.2 Evaluation of Safety

3.2.1 Study M06-826

During the double-blind period through Week 8, there were no statistically significant differences across treatment groups in the overall frequency of AEs, SAEs, deaths, discontinuations, or AEs of special interest. No cases of lymphomas, CHF, demyelinating disease, lupus-like syndrome, or deaths were reported during the DP Period through Week 8. Additionally, no cases of TB were reported.

Among subjects < 40 years of age, a statistically significant difference was observed between the adalimumab 160/80/40 and placebo treatment groups in the frequency of SAEs (2.4% versus 9.2%, respectively; $P = 0.028$). No other statistically significant differences were observed among subgroups: gender (male, female), race (white, non-white).

The most frequently reported AE terms were headache, nasopharyngitis, abdominal pain, fatigue, upper respiratory tract infection, nausea, and injection site pain.

During adalimumab exposure through Week 52, more than 75% of subjects reported at least 1 AE while receiving adalimumab. The most frequently reported AEs of special interest were infections (38.2%), followed by injection site reactions (8.6%). No cases of

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lymphomas, NMSC, lupus-like syndrome, or deaths were reported during any adalimumab exposure. Additionally, no cases of TB were reported.

Infections were reported by 38.2% of subjects during any adalimumab exposure through Week 52. The most frequently reported infections were nasopharyngitis and upper respiratory tract infection.

During any adalimumab exposure through Week 52, the majority of subjects (45/48) reported injection site reactions that were considered possibly or probably related to adalimumab. The most frequently reported injection site reactions were injection site reaction, injection site erythema, injection site pruritus, and injection site pain.

There were no cases of TB reported during the study.

There were no deaths during this study.

3.2.2 Study M06-827

A statistically significantly greater proportion of adalimumab-treated than placebo-treated Subjects reported injection site-related AEs (injection site erythema and injection site reaction) considered possibly or probably relate to study drug.

There were no deaths during this study.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-826
(ITT-A3 Set-NRI)

	Placebo	Adalimumab 80/40		Adalimumab 160/80/40	
Subgroup	Rate	Rate	95% CI	Rate	95% CI
Gender					
Male	7/82 (8.5%)	7/78 (9.0%)	(-8.3%, 9.2%)	13/83 (15.7%)	(-2.8%, 17.0%)
Female	5/48 (10.4%)	6/52 (11.5%)	(-11.1%, 13.4%)	11/47 (23.4%)	(-1.9%, 27.9%)
Age					
<40	9/72 (12.5%)	8/63 (12.7%)	(-11.0%, 11.4%)	16/74 (21.6%)	(-3.0%, 21.2%)
40-64	3/54 (5.6%)	4/59 (6.8%)	(-7.6%, 10.1%)	7/51 (13.7%)	(-3.1%, 19.4%)
≥65	0/4 (0.0%)	1/8 (12.5%)	(-10.4%, 35.4%)	1/5 (20.0%)	(-15.1%, 55.1%)
Race					
White	10/117 (8.5%)	12/119 (10.1%)	(-5.9%, 8.9%)	22/119 (18.5%)	(1.3%, 18.6%)
Non-white	2/13 (15.4%)	1/11 (9.1%)	(-32.2%, 19.7%)	2/11 (18.2%)	(-27.3%, 32.9%)

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Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 8		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Gender			
Male	13/152 (8.6%)	23/142 (16.2%)	(0.1%, 15.2%)
Female	10/94 (10.6%)	18/106 (17.0%)	(-3.1%, 15.8%)
Age			
<40	8/118 (6.8%)	23/136 (16.9%)	(2.4%, 17.9%)
40-64	13/116 (11.2%)	17/105 (16.2%)	(-4.1%, 14.1%)
≥65	2/12 (16.7%)	1/7 (14.3%)	(-33.8%, 31.0%)
Race			
White	23/234 (9.8%)	38/236 (16.1%)	(0.2%, 12.3%)
Non-white	0/12 (0.0%)	3/12 (25.0%)	

Number and Percentage of Subjects with Remission per Mayo Score at Week 52 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 52		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Gender			
Male	18/152 (11.8%)	23/142 (16.2%)	(-3.6%, 12.3%)
Female	3/94 (3.2%)	20/106 (18.9%)	(7.4%, 23.9%)
Age			
<40	11/118 (9.3%)	27/136 (19.9%)	(2.0%, 19.0%)
40-64	9/116 (7.8%)	16/105 (15.2%)	(-0.9%, 15.9%)
≥65	1/12 (8.3%)	0/7 (0.0%)	(-24.0%, 7.3%)
Race			
White	21/234 (9.0%)	38/236 (16.1%)	(1.2%, 13.1%)
Non-white	0/12 (0.0%)	5/12 (41.7%)	(13.8%, 70.0%)

As seen from tables above, in Study M06-826, 95% CIs for the difference in clinical remission at Week 8 between adlimumab 80/40 and placebo included zero for all subgroups.

95% CIs for the difference in clinical remission at Week 8 between adlimumab 160/80/40 and placebo included zero for gender and age,

In Study M06-827, 95% CIs for the difference in clinical remission at Week 8 between adlimumab and placebo excluded zero for male, and age < 40, and, white,

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95% CIs for the difference in clinical remission at Week 52 between adlimumab and placebo excluded zero for female, age < 40, and white and non-white.,

4.2 Other Special/Subgroup Population

Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-826
(ITT-A3 Set-NRI)

Subgroup	Placebo Rate	Adalimumab 80/40 Rate	95% CI	Adalimumab 160/80/40 Rate	95% CI
CRP					
<10.0 mg/L	7/95 (7.4%)	9/87 (10.3%)	(-5.3%, 11.3%)	21/101 (20.8%)	(3.9%, 22.9%)
≥10.0 mg/L	4/32 (12.5%)	4/40 (10.0%)	(-17.3%, 12.3%)	2/25 (8.0%)	(-20.1%, 11.1%)
Corticosteroid Use at baseline					
Yes	8/89 (9.0%)	9/74 (12.2%)	(-6.4%, 12.7%)	12/71 (16.9%)	(-2.6%, 18.5%)
No	4/41 (9.8%)	4/56 (7.1%)	(-13.9%, 8.7%)	12/59 (20.3%)	(-3.1%, 24.3%)
Azathioprine and 6-Mercapto-purine therapy at baseline					
Yes	2/52 (3.8%)	6/51 (11.8%)	(-2.4%, 18.2%)	8/51 (15.7%)	(0.6%, 23.1%)
No	10/78 (12.8%)	7/78 (8.9%)	(-13.7%, 5.8%)	16/79 (20.3%)	(-4.1%, 19.0%)

Number and Percentage of Subjects with Remission per Mayo Score at Week 8 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 8		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Prior Anti-TNF Treatment			
No	16/145 (11.0%)	32/150 (21.3%)	(2.0%, 18.6%)
Yes	7/101 (6.9%)	9/98 (9.2%)	(-5.3%, 9.8%)
CRP			
<10.0 mg/L	20/169 (11.8%)	35/180 (19.4%)	(0.0%, 15.2%)
≥10.0 mg/L	3/77 (3.9%)	6/67 (9.0%)	(-3.0%, 13.1%)
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	12/80 (15.0%)	12/93 (12.9%)	(-12.4%, 8.3%)
No	11/166 (6.6%)	29/155 (18.7%)	(4.9%, 19.3%)

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Corticosteroid Use at baseline			
Yes	13/140 (9.3%)	31/150 (20.7%)	(3.3%, 19.5%)
No	10/106 (9.4%)	10/98 (10.2%)	(-7.4%, 8.9%)

Number and Percentage of Subjects with Remission per Mayo Score at Week 52 by Subgroups
Study M06-827
(ITT Set-NRI)

	Remission per Mayo Score at Week 52		
Subgroup	Placebo Rate	Adalimumab Rate	95% CI
Prior Anti-TNF Treatment			
No	18/145 (12.4%)	33/150 (22.0%)	(1.1%, 18.1%)
Yes	3/101 (3.0%)	10/98 (10.2%)	(0.4%, 14.1%)
CRP			
<10.0 mg/L	18/169 (10.7%)	35/180 (19.4%)	(1.4%, 16.2%)
≥10.0 mg/L	3/77 (3.9%)	8/67 (11.9%)	(-8.4%, 16.9%)
Azathioprine and 6-Mercapto-purine therapy at baseline			
Yes	8/80 (10.0%)	17/93 (18.3%)	(-2.0%, 18.5%)
No	13/166 (7.8%)	26/155 (16.8%)	(1.8%, 16.1%)
Corticosteroid Use at baseline			
Yes	10/140 (7.1%)	25/150 (16.7%)	(2.2%, 16.9%)
No	11/106 (10.4%)	18/98 (18.4%)	(-1.6%, 17.6%)

Complied from Tables 14.2_61.1.1 to 14.2_61.18, 14.2_62.1.1 – 14.2_62.1.18.

As seen from tables above, in Study M06-826, 95% CIs for the difference in clinical remission at Week 8 between adlimumab 80/40 and placebo included zero for all subgroups.

95% CIs for the difference in clinical remission at Week 8 between adlimumab 160/80/40 and placebo included zero for corticosteroid use at baseline subgroups. 95% CI excluded zero for CRP <10.0 mg/L, and Azathioprine or 6-MP use at baseline.

Furthermore, there was inconsistency in the difference in clinical remission at Week 8 between adlimumab 160/80/40 and placebo for CRP (<10.mg/L, ≥10 mg/L) subgroup (13.4% for CRP < 10 mgL vs. -4.5% for CRP ≥10.0 mg/L) (Breslow-Day, p=0.0839).

In Study M06-828, 95% CIs for the difference in clinical remission at Week 8 between adlimumab and placebo excluded zero for no prior Anti-TNF treatment, CRP <10.0 mg/L,and corticosteroid use at baseline.

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Furthermore, there was inconsistency in the difference in clinical remission at Week 8 between adlimumab and placebo for Azathioprine or 6-MP use at baseline (yes vs. no) subgroup (-2.1% for yes vs. 12.1% for no) (Breslow-Day, p=0.0175).

95% CIs for the difference in clinical remission at Week 52 between adlimumab and placebo excluded zero for no prior Anti-TNF treatment, CRP <10.0 mg/L, and corticosteroid use at baseline.

5. SUMMARY AND CONCLUSION

5.1 Statistical Issues and Collective Evidence

Study M06-826

For Study M06-826, in the ITT-A3 set the clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was statistically higher than that in the placebo group (18.5% vs. 9.2%). However, the treatment difference was borderline (p=0.047; Fisher's exact test) and was not robust.

There was no statistically significant difference in clinical remission observed between the adalimumab 80/40 treatment group and the placebo group (p=0.833).

This reviewer performed a post-hoc analysis of the proportion of subjects with remission at Week 8 controlling for Mayo score at baseline using the Cochran-Mantel-Haenszel method. The results revealed that the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score. (p=0.089).

The sponsor stated in Response to Information Request dated May 09, 2011 that due to windowing rules for dosing (±3 days), one subject in adalimumab 160/80/40 had a response attributed to Week 8 in the Observed Case analysis but did not receive the Week 8 dose of adalimumab (i.e., was not a completer). This subject was considered as a "responder" in the sponsor's analysis of primary efficacy endpoint.

In the Response to Information Request dated September 09, 2001, it was stated that three subjects (1 subject in each treatment group) from Study M06-826 were included in the OC (observed case) analysis but not the CC (complete case) analysis for remission at Week 8 because although they had Week 8 evaluations, they did not receive the Week 8 dose of adalimumab and were therefore not considered completers. The subject in adalimumab 160/80/40 treatment group is as follows:

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- **Subject 63951 (adalimumab 160 80/40 treatment group) was a 29-year-old male with a Baseline Mayo score of 6 who received study drug at Week 0 only and was discontinued due to a protocol violation. The subject entered the study with a Mayo score of 6 and after discontinuation the partial Mayo score at Day 54 was reported to be 0.**

So, the remission status of this subject (responder or non-responder) at Week 8 is unclear and debatable..

This reviewer performed the sensitivity analyses to find out how many alternation in the responder status would change 2-sided p-value from the observed p-value to greater than 0.05, keeping sample sizes fixed.

These sensitivity analysis revealed that this study could be a "negative" study, if a change in the responder status of 1 subjects in the adalimumab 160/80/40 group from responder to non-responder , or in the responder status of just 1 placebo subject from non-responder to responder.

In the pre-sBLA meeting dated November 23, 2010, the medical division recommends that the post hoc analysis utilize a definition of clinical remission as total Mayo score ≤ 2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability) and no individual subscore > 1.

However, the sponsor failed to perform the statistical analysis for FDA definition of clinical remission in the submission.

This reviewer performed the post-hoc analysis for FDA definition of clinical remission at Week 8. The new FDA defined clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was numerically higher than that in the placebo group; but, it failed achieved statistical significance. (11.5% vs. 4.6%, p=0.067, Fisher's Exact test).

Furthermore, the results from analyses of secondary endpoints failed to show any statistical significant treatment benefit of adlimumabl 160/80/40 over placebo. Moreover, subgroup analysis based on the CRP showed inconsistent findings. The treatment difference in clinical remission at Week 8 between adalimumab 160/80/40 and placebo was 13.4% for CRP < 10.0 mg/L vs. -4.5% for CRP $\geq$10.0 mg/L, (Breslow-Day, p=0.084).

Study M06-827

For Study M06-826, the clinical remission rates per Mayo score at both Week 8 and Week 52 in the adalimumab 160/80/40 treatment group were statistically higher than that in the placebo group (16.5% vs. 9.3% at Week 8 and 17.3% vs. 8.5% at Week 52).

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The sponsor failed to re-randomize subjects for maintenance phase of this study, as per request by the medical division at phase II meeting.

For Study M06-827, subgroup analysis based on Azathioprine or 6-MP use at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% for yes vs. 12.1% for no (Breslow-Day, p=0.017).

There was disproportionate missing data for subjects for remission per Mayo score at Week 52. More placebo subjects had missing data for remission per Mayo score at Week 52 as compared to adalimumab (202/260 vs. 176/258, p=0.015). Therefore the sponsor's ITT analysis with NRI imputation tends to be biased in favor of adalimumab. With more than 70% subjects with missing data at Week 52, the treatment group difference in remission rate at Week 52 might not be reliable.

There was disproportionate missing data for subjects for sustained remission per Mayo score at Week 8 and Week 52. More placebo subjects had missing data for sustained remission per Mayo score at Week 8 and Week 52 as compared to adalimumab (204/260 vs. 169/258 ; p=0.001). Therefore the sponsor's ITT analysis with NRI imputation tends to be biased in favor of adalimumab. With more than 70% subjects with missing data at Week 8 and Week 52, the treatment group difference in sustained remission rate at Week 8 and Week 52 might not be reliable.

This reviewer performed the post-hoc analyses for the new FDA definition of clinical remission at Week 8, Week 52, and Week 8 and Week 52. For the FDA defined clinical remission, the treatment difference achieved statistical significance at nominal significance level of 0.05 at Week 8 and at Week 52. But, it failed to achieve significance at minor p-value 0.05 at Week 8 and Week 52 (p=0.088).

Furthermore, the sponsor's result on sustained remission per Mayo score at Week 8 and Week 52 is method dependent. The treatment group difference would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.062). Therefore, the results from analysis of sustained remission per Mayo score at Week 8 and Week 52 might not be considered robust.

5.2 Conclusions and Recommendations

Study M06-826

For Study M06-826, in the ITT-A3 set the clinical remission rate per Mayo score at Week 8 in the adalimumab 160/80/40 treatment group was statistically higher than that in the placebo group (18.5% vs. 9.2%, p=0.031). However, the treatment difference was borderline (p=0.047; Fisher's exact test) and was not robust. This treatment difference might not be considered as clinically significant as compared to the other approved biological products. .

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There was no statistically significant difference in clinical remission observed between the adalimumab 80/40 treatment group and the placebo group.

Statistically significant differences were found across treatment groups for Mayo score at baseline in the ITT-A3 Set (chi-square p-value 0.004). This reviewer's post-hoc analysis showed that the treatment difference between the adalimumab 160/80/40 treatment group and the placebo group failed to achieve statistical significance when adjusted for baseline Mayo score. (p=0.089).

Furthermore, the results from analyses of secondary endpoints failed to show any treatment benefit of adlimumabl 160/80/40 over placebo. In the CRP subgroup analysis, an inconsistent treatment effect was shown, (13.4% for CRP < 10.0 mg/L vs. -4.5% for CRP ≥10.0 mg/L) (Breslow-Day, p=0.084).

Study M06-827

For Study M06-827, the clinical remission rates per Mayo score at both Week 8 and Week 52 in the adalimumab 160/80/40 treatment group were statistically higher than that in the placebo group (16.5% vs. 9.3% at Week 8, p=0.019 and 17.3% vs. 8.5% at Week 52, p=0.004). However, this treatment difference might not be considered as clinically significant as compared to the other approved biological products.

The sponsor failed to re-randomize subjects for maintenance phase of this study, as per request by the medical division at phase II meeting.

For Study M06-827, subgroup analysis based on Azathioprine or 6-MP use at baseline (yes vs. no) showed inconsistent treatment difference in clinical remission at Week 8 between adalimumab and placebo; -2.1% for yes vs. 12.1% for no (Breslow-Day, p=0.017).

There was disproportionate missing data for subjects for remission per Mayo score at Week 52. More placebo subjects had missing data for remission per Mayo score at Week 52 as compared to adalimumab (202/260 vs. 176/258, p=0.015). Therefore the sponsor's ITT analysis with NRI imputation would tend to be biased in favor of adalimumab. With more than 70% of subjects with missing data at Week 52, the treatment group difference in remission rate at Week 52 would not be reliable.

Similarly, there was disproportionate missing data for subjects for sustained remission per Mayo score at both Week 8 and Week 52. More placebo subjects had missing data for sustained remission per Mayo score at Week 8 and Week 52 as compared to adalimumab (204/260 vs. 176/258 ; p=0.001). Therefore the sponsor's ITT analysis with NRI imputation would tend to be biased in favor of adalimumab. With more than 70% of subjects with missing data at both Week 8 and Week 52, the treatment group difference in sustained remission rate at Week 8 and Week 52 would not be reliable.

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Furthermore, the sponsor's result on sustained remission per Mayo score at both Week 8 and Week 52 is marginally statistically significant and thus method dependent. The treatment group difference would not achieve statistical significance, if the more conservative statistical method for analyzing binary data, Fisher's Exact test, were used (p=0.062). Therefore, the results from analysis of sustained remission per Mayo score at both Week 8 and Week 52 might not be considered robust.

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Reference ID: 3200370

Reference ID: 3200370

6 APPENDIX

Table 1 Demographic and Baseline Characteristics (ITT-A3 Set) Study M06-826

	PLACEBO (N=130) n (%)	ADALIMUMAB 80/40 MG (N=130) n (%)	ADALIMUMAB 160/80/40 MG (N=130) n (%)	ADALIMUMAB TOTAL (N=260) n (%)	TOTAL (N=390) n (%)	P-VALUE@
SEX						
FEMALE	48 (36.9)	52 (40.0)	47 (36.2)	99 (38.1)	147 (37.7)	0.795
MALE	82 (63.1)	78 (60.0)	83 (63.8)	161 (61.9)	243 (62.3)	
MISSING	0	0	0	0	0	
RACE						
WHITE	117 (90.0)	119 (91.5)	119 (91.5)	238 (91.5)	355 (91.0)	0.882
BLACK	5 (3.8)	6 (4.6)	2 (1.5)	8 (3.1)	13 (3.3)	
ASIAN	5 (3.8)	5 (3.8)	7 (5.4)	12 (4.6)	17 (4.4)	
AMERICAN INDIAN/ALASKA NATIVE	0	0	0	0	0	
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	
OTHER	3 (2.3)	0	2 (1.5)	2 (0.8)	5 (1.3)	
MISSING	0	0	0	0	0	
ETHNICITY						
HISPANIC OR LATINO	5 (3.8)	6 (4.6)	4 (3.1)	10 (3.8)	15 (3.8)	0.812
NO ETHNICITY	125 (96.2)	124 (95.4)	126 (96.9)	250 (96.2)	375 (96.2)	
AGE (YEARS)						
< 40	72 (55.4)	63 (48.5)	74 (56.9)	137 (52.7)	209 (53.6)	0.539
40 - <= 64	54 (41.5)	59 (45.4)	51 (39.2)	110 (42.3)	164 (42.1)	
>= 65	4 (3.1)	8 (6.2)	5 (3.8)	13 (5.0)	17 (4.4)	
MISSING	0	0	0	0	0	

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NICOTINE											
USER	7	(5.4)	8	(6.2)	12	(9.2)	20	(7.7)	27	(6.9)	0.434
EX-USER	35	(26.9)	46	(35.4)	37	(28.5)	83	(31.9)	118	(30.3)	
NON-USER	88	(67.7)	76	(58.5)	81	(62.3)	157	(60.4)	245	(62.8)	
UNKNOWN	0		0		0		0		0		
ALCOHOL											
DRINKER	57	(43.8)	62	(47.7)	62	(47.7)	124	(47.7)	181	(46.4)	0.773
EX-DRINKER	7	(5.4)	5	(3.8)	9	(6.9)	14	(5.4)	21	(5.4)	
NON-DRINKER	66	(50.8)	63	(48.5)	59	(45.4)	122	(46.9)	188	(48.2)	
UNKNOWN	0		0		0		0		0		

Reference ID: 3200370

Table 1 Demographic and Baseline Characteristics (ITT-A3 Set) Study M06-826 (Continued)

	PLACEBO (N=130) n (%)	ADALIMUMAB 80/40 MG (N=130) n (%)	ADALIMUMAB 160/80/40 MG (N=130) n (%)	ADALIMUMAB TOTAL (N=260) n (%)	TOTAL (N=390) n (%)	P-VALUE@
CRP (HIGH SENSITIVITY MG/L)						
< 10.0	95 (74.8)	87 (68.5)	101 (80.2)	188 (74.3)	283 (74.5)	0.104
>=10.0	32 (25.2)	40 (31.5)	25 (19.8)	65 (25.7)	97 (25.5)	
MISSING	3	3	4	7	10	
CONFIRMED ULCERATIVE COLITIS USING BIOPSY RESULTS						
YES	130 (100)	129 (99.2)	130 (100)	259 (99.6)	389 (99.7)	
NO	0	1 (0.8)	0	1 (0.4)	1 (0.3)	
MISSING	0	0	0	0	0	
EVIDENCE OF DYSPLASIA/MALIGNANCY						
YES	0	0	0	0	0	
NO	130 (100)	129 (100)	130 (100)	259 (100)	389 (100)	
MISSING	0	1	0	1	1	

	PLACEBO (N=130) n (%)	ADALIMUMAB 80/40 MG (N=130) n (%)	ADALIMUMAB 160/80/40 MG (N=130) n (%)	ADALIMUMAB TOTAL (N=260) n (%)	TOTAL (N=390) n (%)	P-VALUE@
SITE OF ULCERATIVE COLITIS						
PANCOLITIS	73 (56.2)	70 (53.8)	60 (46.2)	130 (50.0)	203 (52.1)	0.158
DESCENDING COLON	42 (32.3)	48 (36.9)	61 (46.9)	109 (41.9)	151 (38.7)	
OTHER	15 (11.5)	12 (9.2)	9 (6.9)	21 (8.1)	36 (9.2)	
MISSING	0	0	0	0	0	

Reference ID: 3200370

Table 2 Demographic Characteristics (ITT-A3 Set) Study M06-826

VARIABLE	TREATMENT	N	MEAN	SD	MEDIAN	MIN	MAX	P-VALUE@
AGE (YEAR)	PLACEBO	130	38.9	12.68	37.0	19	72	0.101
	ADA 80/40 MG	130	41.6	13.99	40.0	18	75	
	ADA 160/80/40 MG	130	39.2	13.46	36.5	19	75	
	ADALIMUMAB TOTAL	260	39.9	13.81	39.0	19	75	
	TOTAL	390	39.5	13.43	38.0	18	75	
WEIGHT (KG)	PLACEBO	130	78.7	17.42	76.0	50	145	0.247
	ADA 80/40 MG	130	76.8	15.01	75.0	47	124	
	ADA 160/80/40 MG	130	75.5	14.20	77.0	46	112	
	ADALIMUMAB TOTAL	260	76.1	14.60	75.5	46	124	
	TOTAL	390	77.0	15.62	76.0	46	145	
WEIGHT - FEMALE (KG)	PLACEBO	48	72.9	22.34	68.5	50	145	
	ADA 80/40 MG	52	71.9	15.96	67.5	47	120	
	ADA 160/80/40 MG	47	64.6	12.86	60.0	46	100	
	ADALIMUMAB TOTAL	99	68.5	14.96	64.0	46	120	
	TOTAL	147	69.9	17.75	65.0	46	145	
WEIGHT - MALE (KG)	PLACEBO	82	82.1	12.72	82.0	53	117	
	ADA 80/40 MG	78	80.0	13.50	78.0	50	124	
	ADA 160/80/40 MG	83	81.6	10.87	82.0	57	112	
	ADALIMUMAB TOTAL	161	80.9	12.20	80.0	50	124	
	TOTAL	243	81.3	12.37	81.0	50	124	
HEIGHT (CM)	PLACEBO	130	173.1	10.05	174.5	145	193	0.941
	ADA 80/40 MG	130	172.7	9.27	173.0	151	190	
	ADA 160/80/40 MG	130	173.0	9.84	173.0	147	200	
	ADALIMUMAB TOTAL	260	172.9	9.54	173.0	147	200	
	TOTAL	390	172.9	9.70	173.0	145	200	
DURATION OF ULCERATIVE COLITIS (YEARS)								
PLACEBO		130	7.49	7.159	5.35	0.3	34.1	0.243
ADA 80/40 MG		130	8.57	7.511	6.91	0.3	39.7	
ADA 160/80/40 MG		130	8.11	7.247	6.06	0.2	34.4	
ADALIMUMAB TOTAL		260	8.34	7.370	6.34	0.2	39.7	
TOTAL		390	8.06	7.302	6.10	0.2	39.7	

Reference ID: 3200370

Table 3 Baseline Characteristics (Endoscopy, Rectal Bleeding, PGA and Stool Frequency Subscores) (ITT-A3 Set) Study M06-826

	PLACEBO (N=130) n (%)	ADALIMUMAB 80/40 MG (N=130) n (%)	ADALIMUMAB 160/80/40 MG (N=130) n (%)	ADALIMUMAB TOTAL (N=260) n (%)	TOTAL (N=390) n (%)	P-VALUE@
ENDOSCOPY SUBSCORE						
NORMAL OR INACTIVE DISEASE (0)	0	0	0	0	0	0.273
MILD DISEASE (1)	1 (0.8)	0	0	0	1 (0.3)	
MODERATE DISEASE (2)	67 (51.5)	60 (46.2)	73 (56.2)	133 (51.2)	200 (51.3)	
SEVERE DISEASE (3)	62 (47.7)	70 (53.8)	57 (43.8)	127 (48.8)	189 (48.5)	
MISSING	0	0	0	0	0	
RECTAL BLEEDING SUBSCORE						
NORMAL (0)	9 (6.9)	9 (6.9)	14 (10.8)	23 (8.8)	32 (8.2)	0.163
MILD DISEASE (1)	50 (38.5)	34 (26.2)	33 (25.4)	67 (25.8)	117 (30.0)	
MODERATE DISEASE (2)	55 (42.3)	70 (53.8)	61 (46.9)	131 (50.4)	186 (47.7)	
SEVERE DISEASE (3)	16 (12.3)	17 (13.1)	22 (16.9)	39 (15.0)	55 (14.1)	
MISSING	0	0	0	0	0	
PHYSICIAN'S GLOBAL ASSESSMENT (PGA) SUBSCORE						
NORMAL (0)	0	0	1 (0.8)	1 (0.4)	1 (0.3)	0.046*
MILD DISEASE (1)	5 (3.8)	11 (8.5)	7 (5.4)	18 (6.9)	23 (5.9)	
MODERATE DISEASE (2)	92 (70.8)	69 (53.1)	85 (65.4)	154 (59.2)	246 (63.1)	
SEVERE DISEASE (3)	33 (25.4)	50 (38.5)	37 (28.5)	87 (33.5)	120 (30.8)	
MISSING	0	0	0	0	0	
STOOL FREQUENCY SUBSCORE						
NORMAL (0)	1 (0.8)	0	1 (0.8)	1 (0.4)	2 (0.5)	0.669
MILD DISEASE (1)	16 (12.3)	17 (13.1)	20 (15.4)	37 (14.2)	53 (13.6)	
MODERATE DISEASE (2)	39 (30.0)	37 (28.5)	28 (21.5)	65 (25.0)	104 (26.7)	
SEVERE DISEASE (3)	74 (56.9)	76 (58.5)	81 (62.3)	157 (60.4)	231 (59.2)	
MISSING	0	0	0	0	0	

NOTE: SUBJECTS RANDOMIZED TO THE PLACEBO GROUP RECEIVED ADA 40 MG EOW OR ADA 160/80/40 EOW STARTING FROM WEEK 0.
PERCENTAGES CALCULATED ON NON-MISSING VALUES.

@ P-VALUE FOR DIFFERENCES BETWEEN THE TREATMENT GROUPS FROM CHI-SQUARE TEST (OR FISHER'S EXACT TEST IF >= 20% OF THE CELLS HAVE EXPECTED CELL COUNT <5).

***, **, * STATISTICALLY SIGNIFICANT AT 0.001, 0.01, AND 0.05 LEVELS, RESPECTIVELY.

Program Source Code: /chenkz/SDA/Humira/UC/CSR/M06-826/B/14.1/PCMS_RUN/T1050501.sas

Reference ID: 3200370

Table 4 Sensitivity Analysis for Study M06-826

Case 1: Placebo responder rate fixed at the observed rate of 9.2% (12 subjects responded over the total 130 subjects).

Adalimumab160/80/40 responder rate varied.

Number of Adalimumab160/80/40:subjects: 130
Number of Placebo subjects: 130

Number Responded in Numerator of the Responder status		Responder Rate			Fisher's Exact test 2-tailed
Rfaximin	Placebo	Adalimumab	Placebo	Diff	p-value
24	12	18.5%	9.2%	9.3%	0.0471
23	12	17.7%	9.2%	8.5%	0.0681

Case 2: Adalimumab 160/80/40 responder rate fixed at the observed rate of 18.5% (24 subjects responded over the total 130 subjects).

Placebo responder rate varied.

Number of Adalimumab 160/80/40 subjects: 130
Number of Placebo subjects: 130

Number Responded in Numerator of the Responder status		Responder Rate			Fisher's Exact test 2-tailed
Rfaximin	Placebo	Adalimumab	Placebo	Diff	p-value
24	12	18.5%	9.2%	9.3%	0.0471
24	13	18.5%	10.0%	8.5%	0.0748

Reference ID: 3200370

Table 5 Number and Percentage of Subjects Achieving Clinical Remission per New FDA Definition at Week 8

Study M06-826
ITT-A# Analysis Set

	Placebo N = 130	Adalimumab 80/40 N = 130		Adalimumab 160/80/40 N = 130	
Analysis	**n/Total[a] (%)**	**n/Total[a] (%)**	***P* value[b]**	**n/Total[a] (%)**	***P* value[b]**
ITT-A3 (As Observed)	6/121 (5.0)	7/118 (5.9)	0.740	15/122 (12.3)	0.042
Completers[c] (As Observed)	6/120 (5.0)	7/117 (6.0)	0.740	15/121 (12.4)	0.042
ITT-A3 (Multiple Imputation[d])	4.6%	5.7%	0.708	11.7%	0.036

a. Total number of subjects with available data at Week 8.

b. *P* value for differences between active treatment and placebo based on chi-square test (or Fisher's exact test if ≥ 20% of the cells have expected cell count < 5).

c. Completers set includes only subjects who completed Week 8 of the study.

d. Multiple imputation with logistic regression (20 imputations) from PROC MI for missing values.

Note: FDA definition of remission is total Mayo score ≤ 2 with rectal bleeding subscore = 0 (no bleeding), endoscopy subscore = 0 (e.g., no friability), and no individual subscore > 1.

Cross reference: Tables 5_1.1 through 5_1.3

Reference ID: 3200370

Table 6 Demographic and Baseline Characteristics (ITT Analysis Set) Study M06-827

VARIABLE	PLACEBO (N=246) n (%)	ADALIMUMAB 160/80/40 MG (N=248) n (%)	TOTAL (N=494) n (%)	P-VALUE@
SEX				
FEMALE	94 (38.2)	106 (42.7)	200 (40.5)	0.305
MALE	152 (61.8)	142 (57.3)	294 (59.5)	
MISSING	0	0	0	
RACE				
WHITE	234 (95.1)	236 (95.2)	470 (95.1)	0.984
BLACK	4 (1.6)	7 (2.8)	11 (2.2)	
ASIAN	4 (1.6)	1 (0.4)	5 (1.0)	
AMERICAN INDIAN/ALASKA NATIVE	1 (0.4)	0	1 (0.2)	
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	
OTHER	2 (0.8)	2 (0.8)	4 (0.8)	
MULTI RACE	1 (0.4)	2 (0.8)	3 (0.6)	
MISSING	0	0	0	
ETHNICITY				
HISPANIC OR LATINO	7 (2.8)	6 (2.4)	13 (2.6)	
NO ETHNICITY	239 (97.2)	242 (97.6)	481 (97.4)	
AGE (YEARS)				
< 40	118 (48.0)	136 (54.8)	254 (51.4)	0.209
40 - 64	116 (47.2)	105 (42.3)	221 (44.7)	
>= 65	12 (4.9)	7 (2.8)	19 (3.8)	
MISSING	0	0	0	

Reference ID: 3200370

Table 6 Demographic and Baseline Characteristics (ITT Analysis Set) Study M06-827 (continued)

	PLACEBO (N=246) n (%)	ADALIMUMAB 160/80/40MG EOW (N=248) n (%)	TOTAL (N=494) n (%)	P-VALUE@
NICOTINE				
USER	19 (7.8)	20 (8.1)	39 (7.9)	0.959
EX-USER	88 (35.9)	94 (37.9)	182 (36.9)	
NON-USER	138 (56.3)	134 (54.0)	272 (55.2)	
UNKNOWN	1	0	1	
ALCOHOL				
DRINKER	125 (51.0)	132 (53.2)	257 (52.1)	0.624
EX-DRINKER	11 (4.5)	8 (3.2)	19 (3.9)	
NON-DRINKER	109 (44.5)	108 (43.5)	217 (44.0)	
UNKNOWN	1	0	1	

VARIABLE	PLACEBO (N=246) n (%)	ADALIMUMAB 160/80/40MG EOW (N=248) n (%)	TOTAL (N=494) n (%)	P-VALUE@
CRP (HIGH SENSITIVITY MG/L)				
< 10 MG/L	169 (68.7)	180 (72.9)	349 (70.8)	0.308
>= 10 MG/L	77 (31.3)	67 (27.1)	144 (29.2)	
MISSING	0	1	1	
CRP (HIGH SENSITIVITY MG/L)				
< 6 MG/L	138 (56.1)	146 (59.1)	284 (57.6)	0.499
>= 6 MG/L	108 (43.9)	101 (40.9)	209 (42.4)	
MISSING	0	1	1	

Reference ID: 3200370

Table 7 Demographic and Baseline Characteristics (ITT Analysis Set) Study M06-827

VARIABLE	TREATMENT	N	MEAN	SD	MEDIAN	MIN	MAX	P-VALUE@
AGE (YEAR)	PLACEBO	246	41.3	13.22	40.0	18.0	79.0	0.158
	ADALIMUMAB 160/80/40 MG	248	39.6	12.47	38.0	18.0	72.0	
	TOTAL	494	40.4	12.86	39.0	18.0	79.0	
WEIGHT (KG)	PLACEBO	246	77.1	17.31	77.0	40.0	133.0	0.252
	ADALIMUMAB 160/80/40 MG	248	75.3	17.71	73.0	39.0	150.0	
	TOTAL	494	76.2	17.52	74.0	39.0	150.0	
WEIGHT - FEMALE (KG)	PLACEBO	94	67.8	16.21	64.0	40.0	124.0	
	ADALIMUMAB 160/80/40 MG	106	66.7	14.54	65.5	39.0	111.0	
	TOTAL	200	67.2	15.32	64.5	39.0	124.0	
WEIGHT - MALE (KG)	PLACEBO	152	82.9	15.37	81.5	54.0	133.0	
	ADALIMUMAB 160/80/40 MG	142	81.7	17.17	79.0	51.0	150.0	
	TOTAL	294	82.3	16.25	80.0	51.0	150.0	
HEIGHT (CM)	PLACEBO	242	172.8	9.82	173.0	150.0	198.0	0.641
	ADALIMUMAB 160/80/40 MG	243	172.4	9.40	173.0	150.0	196.0	
	TOTAL	485	172.6	9.60	173.0	150.0	198.0	
BODY MASS INDEX (KG/M2)	PLACEBO	242	25.7	5.35	25.1	16.0	45.4	0.353
	ADALIMUMAB 160/80/40 MG	243	25.3	5.37	24.5	15.8	46.4	
	TOTAL	485	25.5	5.36	24.6	15.8	46.4	

VARIABLE	TREATMENT	N	MEAN	SD	MEDIAN	MIN	MAX	P-VALUE@
DURATION OF ULCERATIVE COLITIS (YEARS)	PLACEBO	246	8.52	7.374	6.35	0.3	43.3	0.619
	ADALIMUMAB 160/80/40	248	8.10	7.091	6.09	0.3	43.9	
	TOTAL	494	8.31	7.229	6.18	0.3	43.9	

Reference ID: 3200370

Table 8 Baseline Characteristics (Endoscopy, Rectal Bleeding, PGA and Stool Frequency Subscores) (ITT Analysis Set) Study M06-827

VARIABLE	PLACEBO (N=246) n (%)	ADALIMUMAB 160/80/40MG EOW (N=248) n (%)	TOTAL (N=494) n (%)	P-VALUE@
ENDOSCOPY SUBSCORE				
NORMAL OR INACTIVE DISEASE (0)	0	0	0	0.890
MILD DISEASE (1)	0	0	0	
MODERATE DISEASE (2)	133 (54.1)	132 (53.4)	265 (53.8)	
SEVERE DISEASE (3)	113 (45.9)	115 (46.6)	228 (46.2)	
MISSING	0	1	1	
RECTAL BLEEDING SUBSCORE				
NO BLOOD SEEN (0)	31 (12.7)	21 (8.5)	52 (10.6)	0.352
STREAKS OF BLOOD WITH STOOL LESS THAN HALF THE TIME (1)	66 (26.9)	68 (27.5)	134 (27.2)	
OBVIOUS BLOOD WITH STOOL MOST OF THE TIME (2)	99 (40.4)	114 (46.2)	213 (43.3)	
BLOOD ALONE PASSED (3)	49 (20.0)	44 (17.8)	93 (18.9)	
MISSING	1	1	2	
PHYSICIAN'S GLOBAL ASSESSMENT (PGA) SUBSCORE				
NORMAL (0)	1 (0.4)	2 (0.8)	3 (0.6)	0.509
MILD DISEASE (1)	16 (6.5)	10 (4.0)	26 (5.3)	
MODERATE DISEASE (2)	155 (63.3)	169 (68.0)	323 (65.7)	
SEVERE DISEASE (3)	73 (29.8)	67 (27.1)	140 (28.5)	
MISSING	1	1	2	
STOOL FREQUENCY SUBSCORE				
NORMAL NUMBER OF STOOLS FOR THIS SUBJECT (0)	3 (1.2)	4 (1.6)	7 (1.4)	0.827
1-2 STOOLS MORE THAN NORMAL (1)	15 (6.1)	20 (8.1)	35 (7.1)	
3-4 STOOLS MORE THAN NORMAL (2)	65 (26.5)	66 (26.7)	131 (26.6)	
5 OR MORE STOOLS MORE THAN NORMAL (3)	162 (66.1)	157 (63.6)	319 (64.8)	
MISSING	1	1	2	

NOTE: PERCENTAGES CALCULATED ON NON-MISSING VALUES.
@ P-VALUE FOR DIFFERENCES BETWEEN THE TREATMENT GROUPS FROM CHI-SQUARE TEST (OR FISHER'S EXACT TEST IF >= 20% OF THE CELLS HAVE EXPECTED CELL COUNT <5).

Program Source Code: /engemmx/SDA/Humira/UC/CSR/M06-827/B/14.1/PCMS_RUN/M06827_ENDO.sas

Reference ID: 3200370

Table 9 Number and Percentage of Subjects Achieving Clinical Remission Per New FDA Definition at Week 8, Week 52, and Both Weeks 8 and 52

Study M06-827
ITT Analysis Set

Analysis Set Analysis Endpoint	n/Total[a] (%) Placebo	 Adalimumab	 *P* value[b]
ITT Set			
As Observed			
Remission per Mayo score at Week 8	10/213 (4.7)	23/220 (10.5)	0.024
Remission per Mayo score at Week 52	12/58 (20.7)	31/82 (37.8)	0.031
Sustained remission per Mayo score at Week 8 and Week 52	3/56 (5.4)	10/79 (12.7)	0.158
Completers[c] (As Observed)			
Remission per Mayo score at Week 8	4/54 (7.4)	15/79 (19.0)	0.063
Remission per Mayo score at Week 52	12/56 (21.4)	31/82 (37.8)	0.041
Sustained remission per Mayo score at Week 8 and Week 52	3/54 (5.6)	10/79 (12.7)	0.176
Multiple Imputation[d]	N = 246	N = 248	
Remission per Mayo score at Week 8	4.1%	9.6%	0.019
Remission per Mayo score at Week 52	15.1%	23.5%	0.048
Sustained remission per Mayo score at Week 8 and Week 52	2.2%	5.7%	0.059

Reference ID: 3200370

Table 9 Number and Percentage of Subjects Achieving Clinical Remission Per New FDA Definition at Week 8, Week 52, and Both Weeks 8 and 52 (continued)

Study M06-827
ITT Analysis Set Including Subjects from Sites Excluded from the Original Analysis

Analysis Set Analysis Endpoint	n/Total[a] (%) Placebo	 Adalimumab	 *P* value[b]
ITT Analysis Set Including Subjects from Sites Excluded from the Original Analysis			
As Observed			
Remission per Mayo score at Week 8	10/226 (4.4)	23/228 (10.1)	0.021
Remission per Mayo score at Week 52	12/60 (20.0)	32/86 (37.2)	0.029
Sustained remission per Mayo score at Week 8 and Week 52	3/58 (5.2)	10/82 (12.2)	0.162
Completers[c] (As Observed)			
Remission per Mayo score at Week 8	4/56 (7.1)	15/82 (18.3)	0.064
Remission per Mayo score at Week 52	12/58 (20.7)	32/86 (37.2)	0.037
Sustained remission per Mayo score at Week 8 and Week 52	3/56 (5.4)	10/82 (12.2)	0.180
Multiple Imputation[a]	N = 260	N = 258	
Remission per Mayo score at Week 8	4.0%	9.3%	0.017
Remission per Mayo score at Week 52	13.0%	23.5%	0.009
Sustained remission per Mayo score at Week 8 and Week 52	1.9%	5.5%	0.042

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 125057 **Applicant:** Abbott Laboratories **Stamp Date:** 1/26/11

Drug Name: Humira (adalimumab) **NDA/BLA Type:** Efficacy **Indication:** ulcerative colitis

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	eCTD
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			<40; 40-64; ≥
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).			X	Datasets in eCTD

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.		X		StudyM06-827 was not designed for maintenance of clinical remission.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No efficacy interim analysis planned.
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		NRI, LOCF

Background

Information Requested

Please perform additional sensitivity analyses for primary clinical endpoint for Study M06-826, co-primary endpoints and the 1st ranked secondary endpoint for Study M06-827. These additional sensitivity analyses will include CC (complete case), OC (observed case) and multiple imputation.

March 26, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

BLA:	125057-232
Drug name:	HUMIRA® (adalimumab)
Dosage form:	Subcutaneous injection
Applicant:	Abbott
Resubmission Date:	March 30, 2012
Indication:	Reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
Clinical Pharmacology Reviewer:	Lin Zhou, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang, Ph.D.
Primary Pharmacometrics Reviewer:	Kevin Krudys, Ph.D.
Pharmacometrics Team Leader:	Nitin Mehrotra, Ph.D.
OCP Division:	DCP 3 and DPM
OND Division:	OND/ODE3/DGIEP

Since clinical pharmacology's review on Humira (sBLA 125057/232 Resubmission for adult ulcerative colitis) was closed on 09/17/2012, additional discussions regarding both the number and the wording of PMC/PMR have taken place. This addendum documents the PMCs/PMRs that have been agreed upon between OCP and OND. This addendum only covers those PMCs/PMRs that are related to Clinical Pharmacology (e.g., # 3, 4, and 6).

PMR #3 A safety and pharmacokinetic trial as a substudy of the trial described in PMC #4 to evaluate trough concentrations and antibody levels at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low

adalimumab exposures benefit from an escalation of the dose without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

Final Protocol Submission: 09/2013
Trial Completion: 03/2018
Final Report Submission: 03/2019

PMC #4 Conduct a trial to evaluate efficacy and safety of induction regimens at doses higher than 160/80 mg. In this trial, the efficacy of adalimumab should be assessed with induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect immunogenicity samples and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

Final Protocol Submission: 09/2013
Study/Trial Completion: 03/2018
Final Report Submission: 03/2019

PMC #6 Utilizing a validated anti-adalimumab antibody (AAA) assay as described in PMC #5 (Note: PMC#5, which is requesting a validated AAA assay, is written by reviewers from Office of Biotechnology Products (OBP)) , you should assess the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMC #4, the trial conducted under PMC #7, and other future studies from other regions of the world in this disease population.

Final Protocol Submission: 09/2013
Study/Trial Completion: 03/2018
Final Report Submission: 03/2019

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/s/

LIN ZHOU
10/01/2012

KEVIN M KRUDYS
10/01/2012

NITIN MEHROTRA
10/01/2012

YOW-MING C WANG
10/02/2012

EDWARD D BASHAW
10/02/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA:	125057-232
Drug name:	HUMIRA® (adalimumab)
Dosage form:	Subcutaneous injection
Applicant:	Abbott
Resubmission Date:	March 30, 2012
Indication:	Reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
Primary Pharmacometrics Reviewer:	Kevin Krudys, Ph.D.
Pharmacometrics Team Leader:	Nitin Mehrotra, Ph.D.
Clinical Pharmacology Reviewer:	Lin Zhou, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang, Ph.D.
OCP Division:	DCP 3 and DPM
OND Division:	OND/ODE3/DGIEP

EXECUTIVE SUMMARY

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab is approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic, arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. The Applicant submitted a supplemental biologic license application on January 25, 2011 to seek approval of adalimumab for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The application received a complete response November 21, 2011. One of the concerns was that the appropriate adalimumab dose may not have been adequately selected.

Exposure-response analysis conducted with data from study M06-827 suggested a higher induction dose could achieve a greater treatment effect for the induction of clinical remission. The review further concluded that the dosing regimen for ulcerative colitis has not been fully explored and without a better defined dosing paradigm the clinical efficacy of Humira in ulcerative colitis population can not be considered adequately defined. Please refer to the clinical pharmacology review dated November 1, 2011 for further

details. The contents of this resubmission do not change the conclusions of the original review. The Gastrointestinal Drugs Advisory Committee was convened on Aug 28, 2012. The following is one of the questions asked to the committee:

“Based on the exposure-response data and observed treatment effect presented, has the optimal Humira dose for treatment of moderately to severely active ulcerative colitis (UC) been adequately established? Please comment on the need for further dose exploration. “

The Committee voted 14 (No) to 3 (Yes) concluding that the optimal dose has not been established. Those who voted “No” noted that a higher dose may present a better picture of benefit and risk and that a post-approval dose response is recommended.

POST-MARKERTING COMMITMENTS

1. A trial to evaluate efficacy and safety of an induction regimen at doses higher than 160/80 mg is recommended as a post-marketing commitment. This recommendation is based on the exposure-response analysis conducted by the agency. This analysis indicates that an induction regimen with doses higher than 160/80 mg may provide additional benefit for inducing clinical remission. The protocol should be agreed upon by the agency prior to the initiation of the trial.

2. The immunogenicity assay as not adequate because the original and new imunogencity assays would not evaluate most patient samples appropriately due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement. There fore, there is a need to develop an assay with improved rug tolerance.

   To address this issue, you should develop, qualify and implement and improved validated AAA assay with reduced sensitivity to product interference. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of AAA. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to drug interference. The validated assay should be capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling, Until assays have been developed and validated, patient samples collected from clinic studies should be banked under appropriate storage conditions.

3. The immunogenicity profile for adalimimab has not been adequately assessed. Utilizing a validated AAA assay as described in Item #2 above, you should assess the immunogenicity profile based on post-dose patient samples in which the adalimumab concentrations are not expected to interfere with the immunogenicity assay."

Note: Item 2 and 3 have been communicated to the Sponsor in the CR letter dated November 12, 2011.

LABEL RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough font~~.

12.3 Pharmacokinetics

…

Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed (b) (4)

(b) (4)

Reviewer's comment: Changes were made to be consistent with section 7.4 of the labeling.

PERTINENT REGULATORY BACKGROUND

A supplemental Biologics License Application (sBLA) was received January 25, 2011 to add the indication of reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely acute ulcerative colitis who have had an inadequate response to conventional therapy. A Complete Response was issued on November 21, 2011. Among the reasons for this action were (1) concern that an appropriate dose was not adequately selected for the efficacy trials and (2) the immunogenicity profile for adalimumab was not adequately established. The Applicant's resubmission was submitted on March 30, 2012. In the briefing document for the Gastroenterology Drug Advisory Committee Meeting, the Applicant submitted additional analysis.

RESULTS OF APPLICANT'S ANALYSIS

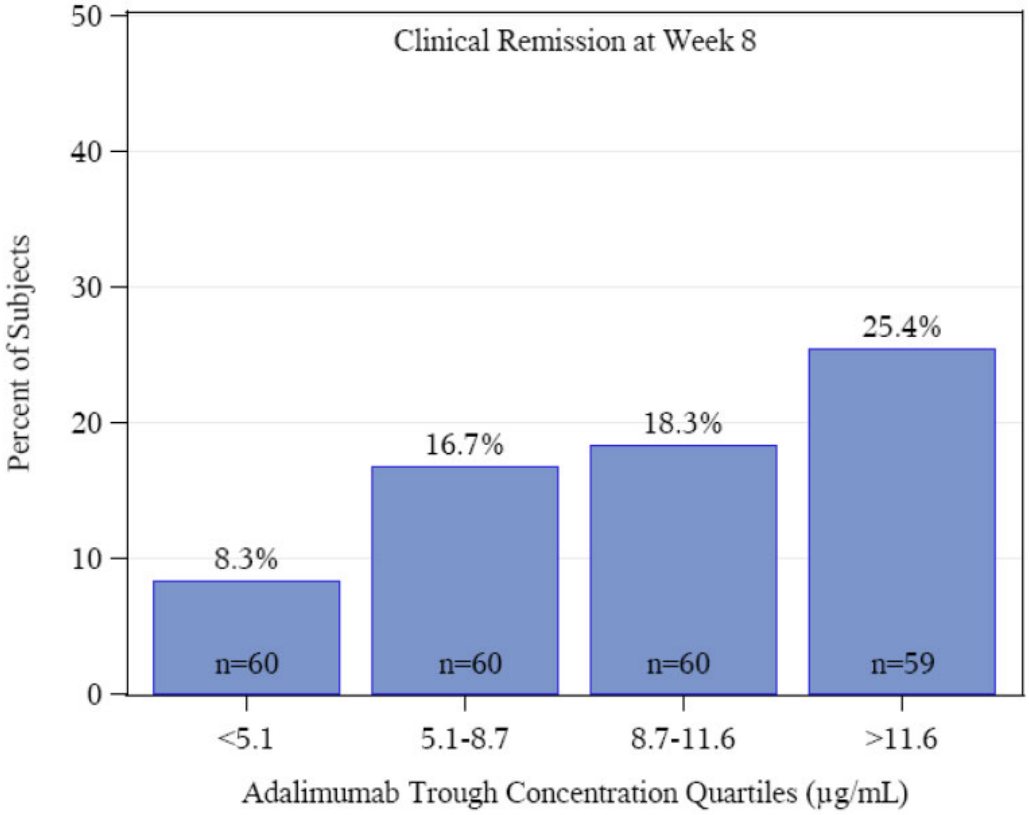
The Applicant conducted various exposure-response analyses using data from Study M06-827 to support their proposed dosing regimen.

Induction Dose Regimen

The percentage of subjects achieving clinical remission (Figure 1) and clinical response (Figure 2) at week 8 was categorized by quartile of week 8 trough serum adalimumab concentration. Logistic regression was used to describe the relationship. In a subgroup analysis, the Applicant noted that the trend of increasing clinical remission with exposure was significant for anti-TNF naïve subjects and inconsistent for anti-TNF experienced

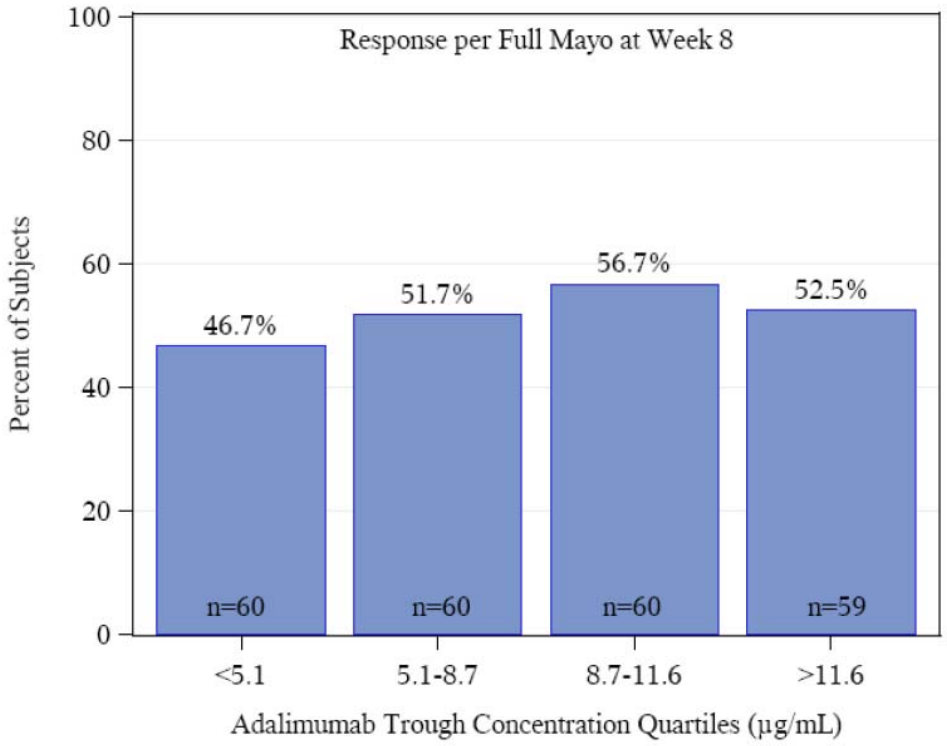
subjects. For clinical response, the relationship with concentration was not statistically significant.

Figure 1: Percentage of Subjects Achieving Clinical Remission at Week 8 by Quartile of Week 8 Adalimumab Trough Concentration (Study M06-827)



Source: Resubmission, Figure 6, Page 92.

Figure 2: Percentage of Subjects Achieving Clinical Response at Week 8 by Quartile of Week 8 Adalimumab Trough Concentration (Study M06-827)



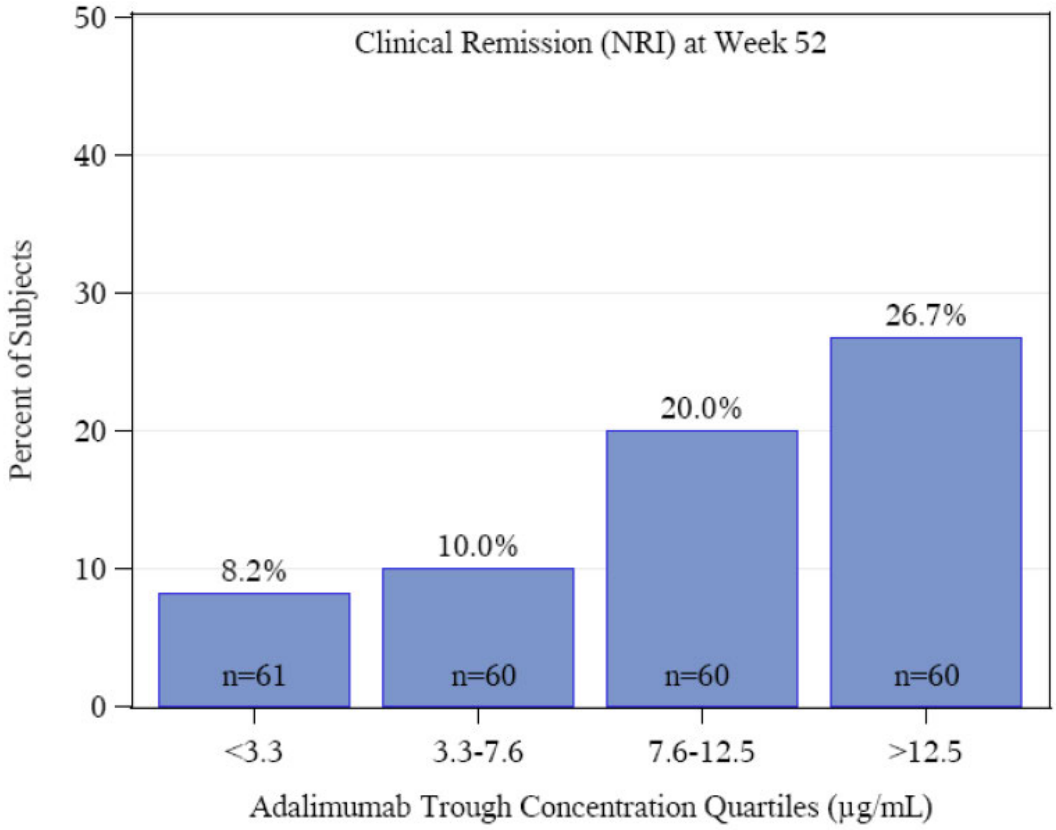
Source: Resubmission, Figure 8, Page 94.

Reviewer's Comments: These analyses are consistent with the reviewer's analysis in the original review of this sBLA and demonstrate an increase in the probability of clinical remission with increasing adalimumab concentration.

Maintenance Dose Regimen

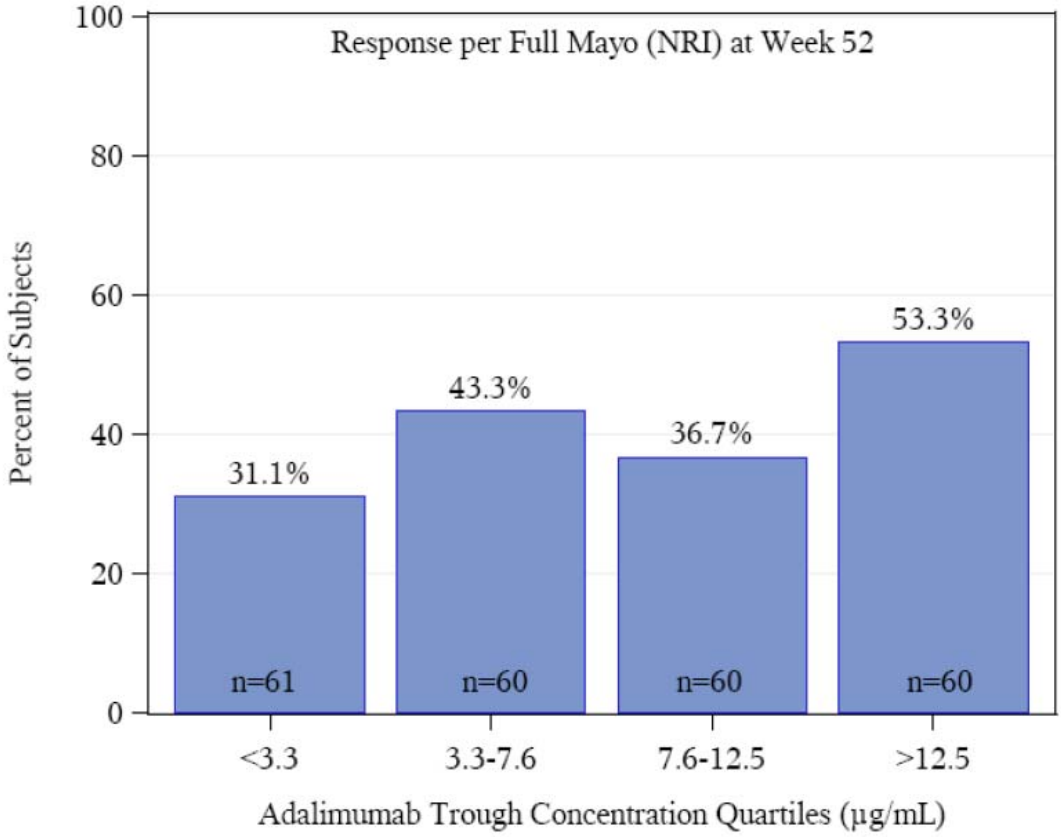
The percentage of subjects with clinical remission (Figure 3) and clinical response (Figure 4) at Week 52 was also plotted against adalimumab trough concentrations. Logistic regression was used to describe the relationship. For this analysis subjects were considered non-remitters or non-responders if they were discontinued or moved to open label prior or if they had a missing Mayo score at the time point of the efficacy assessment. The trough concentration prior to discontinuing, missing Mayo score measurement or moving to open label was used in the analysis. Similar to the induction analysis, the relationship was statistically significant for clinical remission but not clinical response.

Figure 3: Percentage of Subjects Achieving Clinical Remission at Week 52 by Quartile of Adalimumab Trough Concentration (Study M06-827)



Source: Resubmission, Figure 10, Page 96.

Figure 4: Percentage of Subjects Achieving Clinical Response at Week 52 by Quartile of Adalimumab Trough Concentration (Study M06-827)



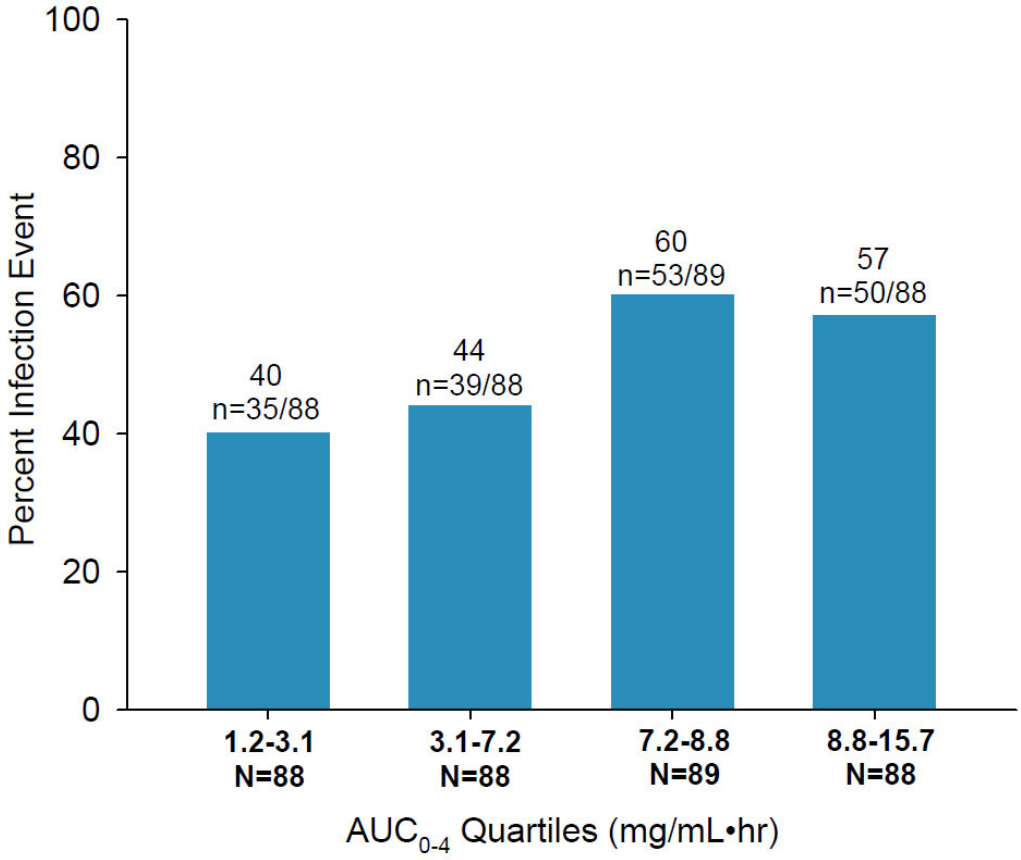
Source: Resubmission, Figure 14, Page 100.

Reviewer's Comments: Please see the original review for a discussion of the limitations of exposure-response analysis for the maintenance dose.

Safety

The relationship between adalimumab exposure and incidence of infection was also examined. AUC from weeks 0 to 4 was used as the exposure metric because this is when expsoure is the highest. First incidence of infection over the entire study period was chosen as the safety response. The Applicant noted a trend of increased infection rate with higher adalimumab exposure (Figure 5).

Figure 5: Percentage of Subjects with Infections by Quartile of Adalimumab AUC_{0-4} (Study M06-827)



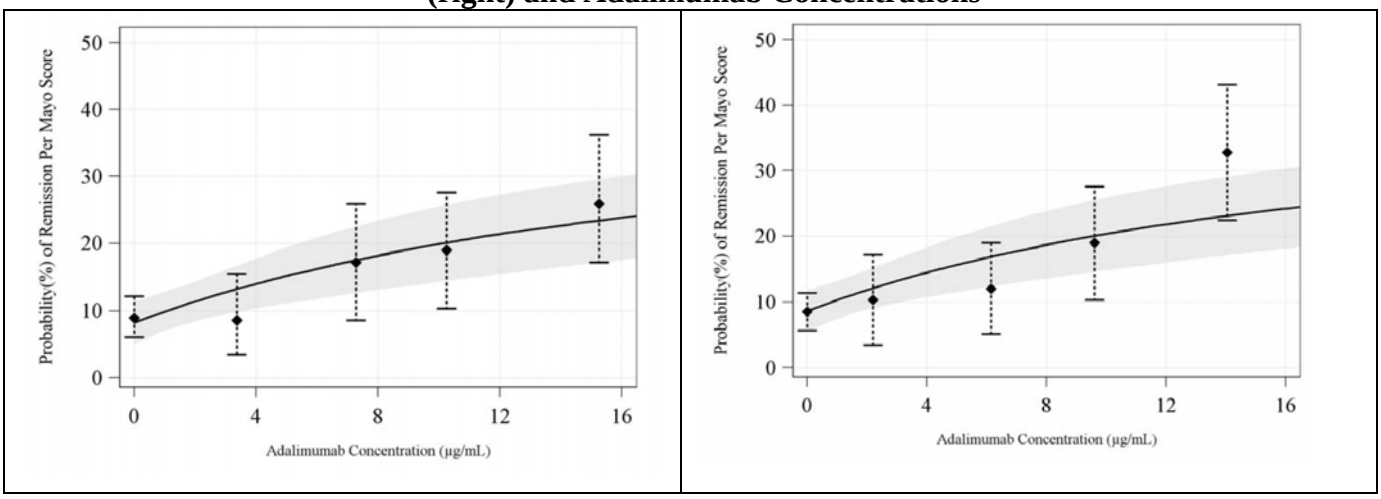
Based on these exposure-response analyses, the Applicant concluded that "an increase in induction dose may increase the overall efficacy at Week 8" but that "the influence of this initial dose on infection rates and other potential AEs is not known at this time."

Reviewer's Comments: Please refer to the original review for a discussion of safety of higher adalimumab exposure.

Advisory Committee Briefing Document

As part of the Advisory Committee Briefing Document, the Applicant presented a new analysis using an E_{max} logistic regression model (Figure 6). This analysis was used to argue that remission and response rates approach a plateau over the range of adalimumab trough concentrations evaluated in the study and thus it is not prudent to explore higher doses with an aim to achieve higher benefit.

Figure 6: Relationship between Clinical Remission at Week 8 (left) and Week 52 (right) and Adalimumab Concentrations



Reviewer's Comments: These new analyses were not included in the resubmission and were therefore not thoroughly reviewed. However, it is important to note the limitation of the Applicant's analyses is the use of an E_{max} logistic regression model to establish the relationship between exposures and induction of clinical remission at Week 8. The observed data from Study 827 indicate that the maximum clinical remission rate is not reached within the observed range of exposures. The E_{max} structure, however, forces the model to predict a plateau for response (induction of clinical remission). Therefore, the choice of E_{max} model may not be appropriate.

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/s/

KEVIN M KRUDYS
09/12/2012

LIN ZHOU
09/12/2012

YOW-MING C WANG
09/12/2012

NITIN MEHROTRA
09/12/2012

EDWARD D BASHAW
09/17/2012

Since this review was placed in DARRTS, additional discussions have taken place regarding both the number and wording of Post-Marketing Commitments and the Final Labeling in light of the recent AC meeting. Internally, a meeting was held with the Clinical Pharmacology Review Team on Sept 17th 2012 to discuss these issues as they relate to the issuance of the final review. The consensus from this meeting was that, while these sections will remain in the current review to capture our current thinking on these issues, a second review (which will be linked to this review) will be placed into DARRTS with both Final Labeling and PMC/PMR language once they have been agreed on between OCP and OND.

CLINICAL PHARMACOLOGY REVIEW

Supplemental BLA:	125057/232.0
Related IND:	100103
Submission Type:	Efficacy Supplement
Brand Name:	Humira®
Drug Name:	Adalimumab
Submission Date:	01/25/2011
PDUFA Goal Date:	11/25/2011
Priority:	Standard
Proposed Indication:	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
Proposed Dosing Regimen	The proposed dose and dosing regimen for induction treatment is an initial dose (Day 1) of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). The proposed dose and dosing regimen for maintenance treatment is doses of 40 mg every other week beginning two weeks after induction treatment (i.e., Day 29).
Sponsor	Abbott
Clin Pharm Reviewer	Lin Zhou, Ph.D.
Clin Pharm Team Leader	Yow-Ming Wang Ph.D.
PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm. D.
OCP Division	DCP 3 and DPM
OND Division	OND/ODE3/DGIP

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1. EXECUTIVE SUMMARY

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), and plaque psoriasis. In this supplemental Biological License Application (sBLA), the Sponsor pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

The sponsor did not conduct phase 2 dose-finding studies and selected the dose and dosing regimen approved for the CD indication for the phase 3 adult UC clinical trials. The proposed dose and dosing regimen for induction treatment is an initial dose (Day 1) of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). The proposed dose and dosing regimen for maintenance treatment is doses of 40 mg every other week beginning two weeks after induction treatment (i.e., Day 29).

Three phase 3 studies were included in this submission: Studies M06-826 (the pivotal induction study), M06-827 (the pivotal maintenance study), and M10-223 (the open-label extension study). The M06-827 study is particularly important for clinical pharmacology review because it was the only study in which PK and immunogenicity data were collected.

Study M06-826 has an 8- or 12-week randomized, double-blind, placebo-controlled period which is followed by open-label treatment through Week 52. The objective was to evaluated adalimumab for the effectiveness of induction treatment. The study enrolled 576 subjects. The primary endpoint was

Reference ID: 3200370

clinical remission per Mayo score which is defined as total Mayo score ≤ 2 and no individual subscore > 1. (Mayo Score is a composite sore of UC disease activity ranging from 0 to 12 based on the sum of 4 sub scores. The higher the score is, the more severe the disease is. The four sub-scores include endoscopy, stool frequency, rectal **bleeding and physician's global asse**ssment.) Week 8 remission rate was 9.2% in the placebo arm and 18.5% in the adalimumab 160/80/40 arm (P=0.031). The adalimumab low dose arm (80/40/40) had a 10.0% clinical remission rate at week 8 which was not significantly different from placebo (P=0.833).

Study M06-827 is a 52-week randomized, double-blind, placebo-controlled, multicenter study which evaluated adalimumab for the effectiveness of induction and maintenance treatment. The study enrolled 518 subjects. The ranked co-primary efficacy endpoints were the proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52. Week 8 remission rate was achieved by 9.3% of subjects in the placebo arm and 16.5% of subjects in the adalimumab 160/80/40 arm (P=0.019). Week 52 remission was achieved in 8.5% of subjects in the placebo arm and 17.3% of subjects in the adalimumab 160/80/40 arm (P=0.004).

Study M10-223 evaluated the long-term maintenance of response, safety and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827.

Exposure-response analysis conducted based on data from study M06-827 suggested a higher induction dose could achieve a greater treatment effect for the induction of clinical remission at week 8. A robust exposure-response relationship could not be established for maintenance phase due to the high dropout rate in the trial and missing PK data.

A required inter-division level Clinical Pharmacology briefing was held on October 21st, 2011.

1.1 Recommendations

Our exposure-response analysis indicates that the dosing has not been fully explored. Without a better defined dosing paradigm the clinical efficacy of Humira in this population can not be considered adequately defined.

No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because majority of the subjects in the phase 3 studies were not tested for anti-adalimumab antibodies due to drug interference. In order to obtain an adequate adalimumab immunogenicity profile, we recommend that the Sponsor (1) develop an assay with improved drug tolerance to allow detecting anti-adalimumab antibodies in the presence of adalimumab drug concentration in the study samples collected from patients during treatment, and/or 2) collect post-dose samples at time points where the adalimumab drug concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL).

From a Clinical Pharmacology perspective, the combination of a lack of adequate dose-response combined with a lack of adequate immunogenicity information will limit our ability to write adequate labeling with regards to the use of this product.

Reference ID: 3200370

1.2 Phase 4 Commitments

Not applicable.

1.3 Summary of Clinical Pharmacology Findings

Evaluation of Proposed Dosing Regimen

The exposure-response relationship for clinical remission at week 8 indicates that the dose range for inducing remission has not been fully explored. This conclusion is derived mainly from two observations. First, there was an increased remission rate with increased exposures that did not plateau at higher exposures. Second, patients with lower exposures in the induction phase were unable to maintain response and switched to open-label treatment earlier than patients with higher exposures. These data suggest that the induction dose studied in the phase 3 program is not optimal and a higher dose for induction may provide better efficacy.

A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Two limitations of the exposure-response are (1) the analysis was based on only 78 patients (31% of the total treatment population) who remained in double-blind phase throughout the trial and had PK data and (2) the analysis dataset included non-responders (i.e., non-remitters) at week 8. Furthermore, only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline mayo score and prior anti-TNF use. While dose escalation was allowed in the trial, the study design does not permit evaluation of the effect of dose escalation on efficacy.

Basic Adalimumab Pharmacokinetics in Adult UC Patients

The PK profile of adalimumab has been characterized in healthy subjects and patients with rheumatoid arthritis. The mean terminal half life was ~ 14 days, ranging from 10 to 20 days across studies. Detailed info is available in the current labeling of HUMIRA® (adalimumab). In this submission, only Ctrough was measured. At Week 4, the mean ± SD serum concentrations of adalimumab in UC subjects were (11.8 ± 3.95 μg/mL) following the induction dose of 160 mg/80 mg administered at Week 0/Week 2. During the maintenance period, the mean ± SD serum trough concentrations of adalimumab in UC subjects were (7.97 ± 6.09 μg/mL at Week 52) after receiving a maintenance dose of 40 mg every other week. The adalimumab concentrations at Week 52 were approximately double (15.0 ± 8.75 μg/mL) in subjects who dose escalated to 40 mg ew compared to those who received 40 mg eow.

Impact of Immunogenicity on Adalimumab Pharmacokinetics

No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only very small number of subjects had confirmed antibody status. The assessment of immunogenicity incidence was not adequate in the current submission. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration (≥ 2 mcg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients.

Reference ID: 3200370

Date: 10/27/2011

Lin Zhou, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Date: 10/26/2011

Nitin Mehrotra, Ph.D.
Pharmacometrics Reviewer
Division of Pharmacometrics
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Date: 10/27/2011

Yow-Ming Wang, Ph.D.
Clinical Pharmacology Team Leader
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Date: 10/27/2011

Christine Garnett, Pharm. D.
Pharmacometrics Team Leader
Division of Pharmacometrics
Office of Clinical Pharmacology

Date: 10/27/2011

E. Dennis Bashaw, Pharm. D.
Division Director
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Reference ID: 3200370

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is the relevant regulatory history for the proposed drug product?
HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adalimumab was initially approved for the treatment of rheumatoid arthritis on December 31, 2002 and was subsequently approved for treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis.

At the Pre-Phase 3 meeting held in June 2006, the FDA provided comments on the overall UC development plan. On 11 August 2006, Abbott submitted the amended phase 3 protocol for FDA review. On 13 September 2006, Abbott and the FDA held a teleconference to provide the FDA with clarifications regarding the clinical design of Study M06-826. At the conclusion of the meeting, the FDA confirmed that Abbott could proceed with Study M06-826 without changes to the protocol.

In addition, in a letter dated 05 September 2008 the FDA provided comments on the statistical analysis plans (SAPs) for the interim analysis (primary endpoint analysis) of Study M06-826. Those comments were addressed in the final version of the Study M06-826 SAP. In another letter dated 24 May 2010, the FDA provided comments on the SAP for Study M06-827 regarding the definition of the ITT population and re-randomization at Week 8. The comment regarding the definition of the ITT was addressed in the final version of the Study M06-827 SAP.

On November 23, 2010, a meeting was held between the sponsor and the Agency regarding the submission of a supplemental BLA for the use of adalimumab in adult patients with moderately to severely active UC.

In this supplemental Biological License Application (sBLA), submitted on Jan 25, 2011, the Sponsor pursues the approval of adalimumab with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy, based on clinical data from three studies (Studies M06-826 [induction study], M06-827 [maintenance study], and M10-223 [open label study]).

2.1.2 What is the formulation?
HUMIRA® (adalimumab) Injection are solution for subcutaneous use. Commercially available dosage forms and strengths are,

1. 40 mg/0.8 mL in a single-use prefilled pen (HUMIRA Pen)
2. 40 mg/0.8 mL in a single-dose prefilled glass syringe
3. 20 mg/0.4 mL in a single-dose prefilled glass syringe

2.1.3 What is the proposed mechanism of action?
From Current Humira Labeling, Section 12.1 Mechanism of Action,

> Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.

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Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10-10M).

2.1.4 What is the proposed indication?
Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

2.1.5 What is the proposed dose and dosing regimen?
Initial dose (Day 1) is 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.

2.2 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
In this submission, the severity of UC was assessed by Mayo Score. Mayo Score is a composite sore of UC disease activity ranging from 0 to 12 based on the sum of 4 sub scores. The higher the score is, the more severe the disease is. The four sub-scores include endoscopy, stool frequency, rectal bleeding and **physician's global assessment. Partial Mayo score** does not include the endoscopy sub-score.

The clinical development program for adalimumab in subjects with moderately to severely active UC (defined as a Mayo score of 6 to 12 points with endoscopy subscore of 2 to 3 points) included a pivotal induction study (Study M06-826), a pivotal maintenance study (Study M06-827), and a supportive long-term open-label extension study (Study M10-223); see list of studies in Appendix 1. M10-223 is currently ongoing. A data cut-off of 31 December 2009 was used for the efficacy and safety data included from Study M10-223 in the analyses for this submission. Pharmacokinetic (PK) and immunogenicity data were collected only in Study M06-827.

Summary of dose regimens studied in the clinical trials:
The sponsor did not conduct phase 2 dose-finding studies and selected the dose and dosing regimen approved for the CD indication and the **exposure-response of adalimumab in Crohn's disease** for the phase 3 adult UC clinical trials. No basis was provided by the sponsor as to why the doses (and thus the response) for UC and CD should be expected to be the same.

The sponsor studied two different induction dosing regimens in the first placebo-controlled phase 3 study: (1) 160/80 mg: initial dose (Day 1) is 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15) and (2) 80/40 mg: initial dose (Day 1) is 80 mg, followed by 40 mg two weeks later (Day 15). The 160/80 mg regimen was studied in the second phase 3 study. The second placebo-controlled phase 3 study studied 160/80 mg induction regimen. Both studies evaluated maintenance dose of 40 mg every other week which began two weeks later (Day 29).

Summary of individual studies:
Study M06-826

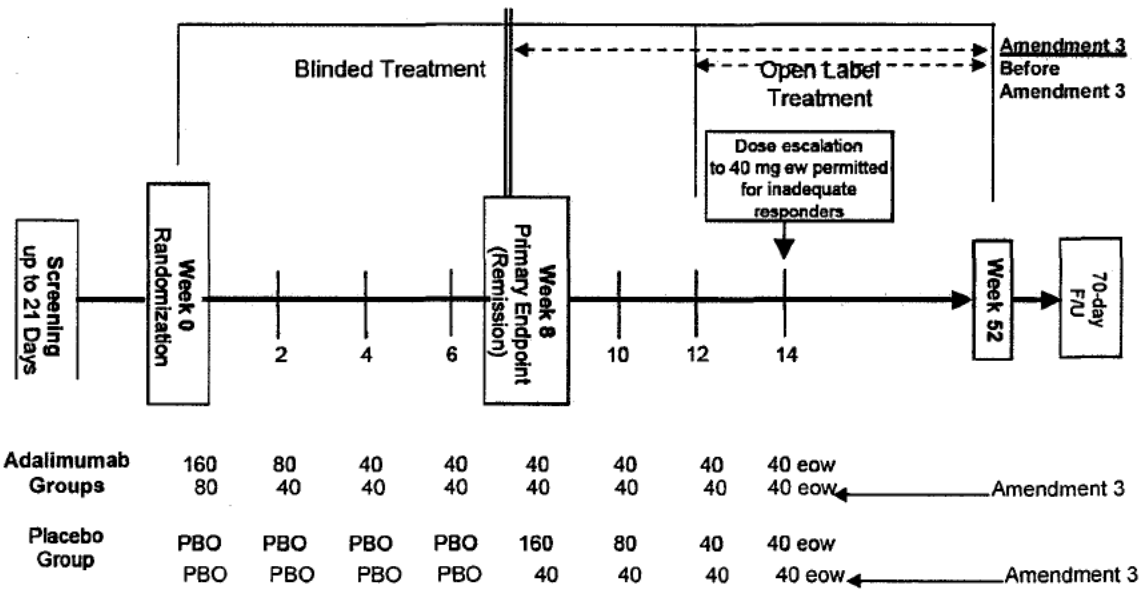
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Study M06-826 comprised of 8- or 12-week randomized, double-blind, placebo-controlled period followed by open-label treatment through Week 52. A schematic of the study design is shown in Figure 1. The study enrolled 576 subjects. Two induction dose levels (160/80 mg and 80/40 mg) were studied in Study M06-826.

Subjects enrolled in the study under the original protocol or Amendments 1 and 2 were randomized in a 1:1 ratio to receive adalimumab or placebo during the 12-week double-blind induction period. Subjects received 160 mg of adalimumab or placebo at Baseline; 80 mg adalimumab or placebo at Week 2; and 40 mg adalimumab or placebo at Weeks 4 and 6. At Week 8, subjects randomized to placebo received 160 mg adalimumab followed by 80 mg adalimumab at Week 10. Subjects randomized to adalimumab continued to receive 40 mg adalimumab at Weeks 8 and 10. All subjects continued to receive 1 injection of open-label adalimumab 40 mg eow beginning at Week 12 up to Week 52 (or the ET visit).

In August 2007, the study design was amended (Amendment 3) to incorporate an additional adalimumab induction dosing arm of 80/40 mg because earlier that year, both 160/80/40 mg and 80/40 mg induction regimens had been approved in the EU as induction treatment for CD. Subjects enrolled in the study after Amendment 3 were randomized in a 1:1:1 ratio to receive 1 of 2 induction regimens of adalimumab or placebo during the 8-week double-blind induction period.

Figure 1. Study Design Schematic (M06-826)
Note: The start of open label treatment phase changed from week 12 to week 8 since Amendment 3.
(Recreated based on Module 5.3.5.1.3, Study 826 Study Report, page 119 /3375 and page 121/3375)



For the assessment of disease activity, subjects underwent colonoscopy or flexible sigmoidoscopy during the Screening period and a flexible sigmoidoscopy at Weeks 8 and 52 (or the early termination [ET] visit).

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Subjects who have inadequate response are permitted to dose escalate to open-label adalimumab 40 mg ew at or after Week 12 or 14. Inadequate response is defined as:

1) Subject with a Baseline Partial Mayo Score of 4-7 who presents with a Partial Mayo Score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart.
2) Subject with a Partial Mayo Score of 8 or 9 at Baseline who presents with a Partial Mayo Score ≥ 7 on 2 consecutive visits at least 14 days apart.

Subjects with persistent inadequate response while on adalimumab 40 mg weekly may be discontinued from the study at the discretion of the investigator.

Study M06-827

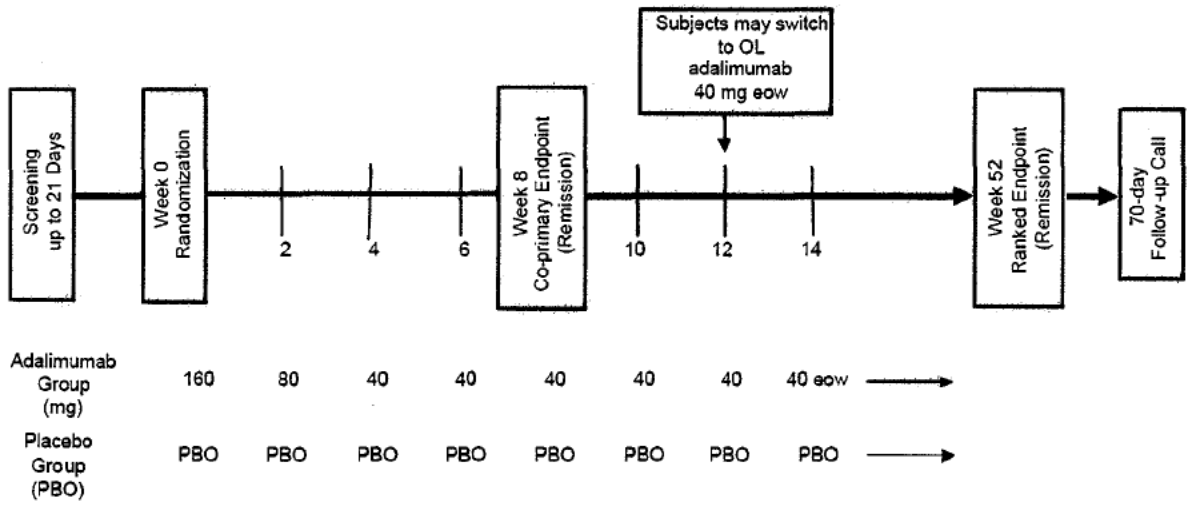
This is a 52-week randomized, double-blind, placebo-controlled, multicenter study. The study enrolled 518 subjects. The ranked co-primary efficacy endpoints were the proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52.

Subjects were stratified by prior exposure to infliximab and/or other anti-TNF agents (golimumab n=2, cetrolizumab n=1), and randomized 1:1 to receive adalimumab or placebo by subcutaneous injection. Subjects assigned to the adalimumab treatment arm received 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week (eow) between Weeks 4 and 50. Subjects assigned to the placebo treatment arm received matching placebo during the same period of time.

Subjects who met the pre-defined criteria for inadequate response (same as those for Study M08-826) could switch to open-label adalimumab 40 mg eow beginning at Week 12, and could further dose escalate to adalimumab 40 mg weekly if they continued to demonstrate inadequate response. Subjects with persistent inadequate response while on adalimumab 40 mg weekly may be discontinued from the study at the discretion of the investigator.

A schematic of the study design is shown in Figure 2.

Figure 2. Study Design of Study M06-827
(Source: Module 5.3.5.1.4 Study 827 Final Protocol page 1530/1630)



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PK assessment:
Blood samples were collected from all subjects immediately prior to dosing at Weeks 0 (Baseline), 2, 4, 8, 32, and 52 (or Early Termination Visits) for adalimumab assay,

Immunogenicity assessment:

- Blood samples were collected from all subjects prior to dosing at Weeks 0 (Baseline), 8, 32, and 52 (or Early Termination Visits) for anti-adalimumab antibody (AAA) assay.
- Blood samples were also collected for infliximab and human anti-chimeric antibody (HACA) assays at Week 0 (Baseline).

Study M10-223
This open-label study is to evaluate the long-term (up to 240 weeks) maintenance of response, safety and tolerability of repeated administration of adlimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827.

2.2.2 What are the endpoints in clinical pharmacology and clinical studies?
Table below listed definitions efficacy-related measures and endpoints.
(Source: Module 2.5. Clinical Overview, page 19/50)

Term	Definition
Mayo score	Composite score of UC disease activity based on the subscores of stool frequency (0 – 3), rectal bleeding (0 – 3), physician's global assessment (0 – 3) and endoscopy (0 – 3). This score ranges from 0 to 12 points with higher scores representing more severe disease.
Partial Mayo score	Composite score of UC disease activity based on the subscores of stool frequency, rectal bleeding, and physician's global assessment and DOES NOT include the endoscopy subscore. This score ranges from 0 to 9 points.
Clinical remission per Mayo score	Mayo score ≤ 2 with no subscore > 1.
Clinical response per Mayo score	A decrease in Mayo score of ≥ 3 points and ≥ 30% from Baseline PLUS a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1.
Mucosal healing	Endoscopy subscore of 0 or 1.
IBDQ response	A ≥ 16-point increase from Baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score.

For the induction study (Study M06-826), the primary efficacy endpoint was clinical remission per Mayo score at Week 8. For maintenance study (Study M06-827), the ranked co-primary efficacy endpoints of were clinical remission per Mayo score at Week 8 and at Week 52.

Secondary efficacy endpoints evaluated throughout Studies M06-826, M06-827, and M10-223 included clinical remission per partial Mayo score, clinical response per Mayo score and partial Mayo score, change from Baseline in Mayo score and partial Mayo score, change from Baseline in Mayo subscores, mucosal healing (endoscopy subscore ≤ 1), rectal bleeding score ≤ 1, **physician's global** assessment score ≤ 1, stool frequency score ≤ 1, health care resource utilization survey, and patient-

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reported outcomes including the Inflammatory Bowel Disease Questionnaire, Short Form-36 Health Survey, Work Productivity and Activity Impairment questionnaire.

According to the non-remission imputation analysis method, all missing response (or remission) values were considered as non-response (or non-remission). Subjects who dose escalated to adalimumab 40 mg weekly were considered as non-responders (or non-remitters) after their dose escalation.

2.2.3 What are the efficacy and safety results in the pivotal studies (Study 826 and 827)?
Table 1 summarizes sponsor's efficacy results (induction and maintenance of clinical remission) from the pivotal trials (Study M06-826 and M06-827).

Table 1. Clinical Remission per Mayo Score in Studies M06-826 and M06-827 by NRI method
Source: Module 5.3.5.1.3, Study 826 Study Report, page 698/3375 and Module 5.3.5.1.4, Study 827 Study Report pages 757, 761 and 765/3632)

Study	Evaluation Time	Clinical remission per Mayo Score	
		160/80 mg vs. Placebo	80/40 mg vs. Placebo
M06-826	Week 8	18.5% vs. 9.2% (p = 0.031, N = 130 vs. 130)	10.0% vs. 9.2% (p = 0.833, N = 130 vs. 130)
M06-827	Week 8	16.5% vs. 9.3%, (p = 0.019, N = 248 vs. 246)	NA
	Week 52	17.3% vs. 8.5%, (p = 0.004, N = 248 vs. 246)	NA
	Sustained at both Weeks 8 and 52	8.5% vs. 4.1%, (p = 0.047, N = 248 vs. 246)	NA

NRI: Non-remitter Imputation

2.2.3.1 Efficacy analysis for induction

Results of Sponsor's Analysis:
In Study M06-826, week 8 remission rate was 9.2% in the placebo arm and 18.5% in the adalimumab 160/80/40 arm (P=0.031). The adalimumab low dose arm (80/40/40) had a 10.0% clinical remission rate at week 8 which was not significantly different from placebo (P=0.833). Based on the above data, the sponsor selected 160/80 for the induction dose for the pivotal maintenance study (M06-827).

Results from Study M06-827 showed that a higher percentage of patients in the adalimumab treatment group, compared with the placebo group, achieved clinical remission per mayo score at Week 8 (16.5% versus 9.3%, p = 0.019).

The sponsor concluded that these data demonstrate that adalimumab 160/80/40 was an effective regimen for the induction of clinical remission after 8 weeks of treatment, while the adalimumab 80/40/40 regimen did not induce clinical remission after 8 weeks.

Reviewer's Assessment:
The pharmacometrics reviewer conducted an independent exposure-response analysis for induction efficacy based on PK data from Study M06-827. The result indicates that a higher dose for the induction phase may provide greater benefit. See Section 1.1.2 of the appended pharmacometric review for details.

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2.2.3.2 Efficacy analysis for Maintenance

Results of Sponsor's Analysis:
In Study M06-827, the ranked co-primary efficacy endpoints were the proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52. Week 8 remission was achieved in 9.3% of subjects in the placebo arm and 16.5% of subjects in the adalimumab 160/80/40 arm (P=0.019). Week 52 remission was achieved in 8.5% of subjects in the placebo arm and 17.3% of subjects in the adalimumab 160/80/40 arm (P=0.004). The first ranked secondary endpoint was sustained clinical remission per Mayo score at both Weeks 8 and 52. This endpoint was achieved by 4.1% of subjects in the placebo arm and 8.5% of subjects in the adalimumab 160/80/40 arm (p=0.047).

According to the sponsor's analysis, a higher percentage of patients in the adalimumab treatment group, compared with the placebo group, achieved both ranked co-primary endpoints (clinical remission per Mayo score at Week 8 [16.5% versus 9.3%, $p = 0.019$] and clinical remission per Mayo score at Week 52 [17.3% versus 8.5%, $p = 0.004$]) and the first ranked secondary endpoint (sustained clinical remission per Mayo score at both Weeks 8 and 52 [8.5% versus 4.1%, $p = 0.047$]).

Reviewer's Assessment:
The pharmacometrics reviewer conducted an independent exposure-response analysis for maintenance of efficacy based on PK data from Study M06-827. But, a robust exposure-response relationship could not be established due to small dataset as a result of significant dropout and missing PK data in the maintenance phase. See Section 1.1.3 of the appended pharmacometric review for details.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?
Exposure-safety analysis was not conducted for adu**lt UC subjects though such an analysis in Crohn's** disease subjects did not show a relationship between exposure and safety (see BLA 125057 clinical pharmacology review by Drs. Tien Mien Chen and Christoffer W. Tornoe for more details).

Summarized below are the sponsor's analyses of the dose-response for safety for the induction phase and comparison of adverse events in placebo vs. adalimumab for the maintenance phase.
The safety of adalimumab in the treatment of subjects with moderately to severely active UC was analyzed using the following integrated analysis sets:

- **Induction Set (N = 1093) – double-blind treatment period between Week 0 and Week 8 for all** subjects who received at least 1 dose of randomized double-blind adalimumab 80/40 (initial dose of 80 mg followed by 40 mg every other week), adalimumab 160/80/40 (initial dose of 160 mg, a second dose of 80 mg after 2 weeks, and 40 mg every other week thereafter), or placebo in Study M06-826 or Study M06-827.
- **Maintenance Set (N = 457) – double-blind treatment pe**riod between Week 8 and Week 52 for all subjects who received at least 1 dose of randomized double-blind adalimumab (160/80/40) or placebo between Week 8 and Week 50 in Study M06-827.
- **All Adalimumab Set (N = 995) – double-blind and open-label** treatment with adalimumab from Week 0 through last dose in Study M06-826 and Study M06-827 and the cutoff date for Study M10-223 (31 December 2009) for all subjects who received at least 1 dose of adalimumab (double-blind or open-label) in Studies M06-826, M06-827, and M10-223.

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Table 2a and 2b summarize the treatment-emergent adverse events in the Induction and Maintenance Set reported by the Sponsor.

Table 2a. Overview of Treatment-Emergent Adverse Events
(Source: Module 2.5 Clinical Overview, Page 37 of 50)

	Number (%) of Subjects				
	Induction Set			Maintenance Set	
Subjects with:	**Placebo N = 483**	**Adalimumab 80/40 N = 130**	**Adalimumab 160/80/40 N = 480**	**Placebo N = 223**	**Adalimumab 160/80/40 N = 234**
Any AE	282 (58.4)	70 (53.8)	265 (55.2)	152 (68.2)	172 (73.5)
Any AE at least possibly drug related[a]	112 (23.2)	28 (21.5)	110 (22.9)	48 (21.5)	72 (30.8)[b]
Any severe AE	41 (8.5)	9 (6.9)	35 (7.3)	16 (7.2)	24 (10.3)
Any serious AE	40 (8.3)	5 (3.8)	25 (5.2)	11 (4.9)	15 (6.4)
Any serious AE at least possibly drug related[a]	7 (1.4)	1 (0.8)	5 (1.0)	2 (0.9)	1 (0.4)
Any AE leading to study drug discontinuation	32 (6.6)	8 (6.2)	23 (4.8)	14 (6.3)	12 (5.1)
Any AE at least possibly drug related leading to discontinuation	7 (1.4)	3 (2.3)	5 (1.0)	7 (3.1)	2 (0.9)
Any AEs leading to death	0	0	0	0	0
AEs of special interest:					
Any allergic reaction	1 (0.2)	0	4 (0.8)	1 (0.4)	2 (0.9)
Any injection site reaction	15 (3.1)	7 (5.4)	30 (6.3)[c]	3 (1.3)	16 (6.8)[d]
Any opportunistic infection (excluding TB)	2 (0.4)	0	5 (1.0)	1 (0.4)	2 (0.9)
Any congestive heart failure	0	0	0	0	1 (0.4)
Any demyelinating disease	0	0	0	0	0
Any lupus-like syndrome	0	0	0	0	1 (0.4)

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Table 2b. Overview of Treatment-Emergent Adverse Events (continued)
(Source: Module 2.5 Clinical Overview, Page 38 of 50)

	Number (%) of Subjects				
	Induction Set			Maintenance Set	
Subjects with:	Placebo N = 483	Adalimumab 80/40 N = 130	Adalimumab 160/80/40 N = 480	Placebo N = 223	Adalimumab 160/80/40 N = 234
Any malignancy	2 (0.4)	0	1 (0.2)	0	1 (0.4)
Any lymphoma	0	0	0	0	0
Any NMSC	1 (0.2)	0	1 (0.2)	0	0
Any malignancy excluding lymphoma and NMSC	1 (0.2)	0	0	0	1 (0.4)
Any malignancy including lymphoma, excluding NMSC	1 (0.2)	0	0	0	1 (0.4)
Any infectious AE	89 (18.4)	26 (20.0)	82 (17.1)	68 (30.5)	89 (38.0)
Any serious infection	7 (1.4)	2 (1.5)	3 (0.6)	1 (0.4)	1 (0.4)
Any hematological event	1 (0.2)	2 (1.5)	6 (1.3)	0	1 (0.4)
Any hepatic event	3 (0.6)	1 (0.8)	10 (2.1)	5 (2.2)	5 (2.1)
Any vasculitis event	0	0	0	0	0
Any diverticulitis event	0	0	0	0	0
Any intestinal perforation event	1 (0.2)	0	0	0	0
Any interstitial lung disease	0	0	0	0	0
Any Stevens-Johnson syndrome	0	0	0	0	0
Any pancreatitis event	0	0	0	1 (0.4)	0
Any UC worsening/flare	59 (12.2)	10 (7.7)	35 (7.3)[e]	37 (16.6)	39 (16.7)

a. As assessed by investigator.
b. $P = 0.026$ for comparison with placebo using Fisher's exact test.
c. $P = 0.022$ for comparison between placebo and adalimumab 160/80/40 using Fisher's exact test.
d. $P = 0.004$ for comparison with placebo using Fisher's exact test.
e. $P = 0.012$ for comparison between placebo and adalimumab 160/80/40 using Fisher's exact test.

Reviewer's interpretation of Table 2a and 2b:

There were few differences between placebo and adalimumab treatment in either the Induction Set or the Maintenance Set in terms of the incidence of different types of adverse events (AEs). Except injection site reactions, none of other type AEs showed a clear trend of higher incidence with increasing dose of adalimumab.

The incidence of injection site reactions in the 160/80/40 treatment, 80/80/40 treatment, and placebo groups were 6.3%, 5.4% and 3.1%, respectively, during the induction period. The incidence was statistically significantly higher in patients receiving adalimumab 160/80/40-treated compared with placebo in the induction period (6.3% versus 3.1%) as well as the maintenance period (6.8% versus 1.3%).

The incidence of AE at least possibly drug related was statistically significantly greater in patients receiving adalimumab 160/80/40 treatment compared with placebo during the maintenance period (30.8% versus 21.5%) but was similar in the 160/80/40 treatment, 80/40/40 treatment and placebo groups during the induction period.

The incidence of UC worsening/flaring was statically significantly lower in the adalimumab 160/80/40 group compared with placebo in the induction period (7.3% versus 12.2%) but was similar in these 2 groups during the maintenance period (16.7% versus 16.6%).

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In addition, the incidence of infectious AE was numerically higher in patients receiving adalimumab 160/80/40 compared with placebo during the maintenance period (38% versus 30.5%). But, it is similar in the 160/80/40 treatment, 80/40/40 treatment, and placebo groups during the induction period (17.1% versus 20% versus 18.4%). A similar pattern was observed in the incidence of any AEs.

In summary, except injection site reactions, there was no increasing incidence of other adverse events with increasing doses.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (concentration-response) for efficacy?

The proposed dose and dosing regimen for induction treatment is an initial dose (Day 1) of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). The proposed dose and dosing regimen for maintenance treatment is doses of 40 mg every other week beginning two weeks after induction treatment (i.e., Day 29).

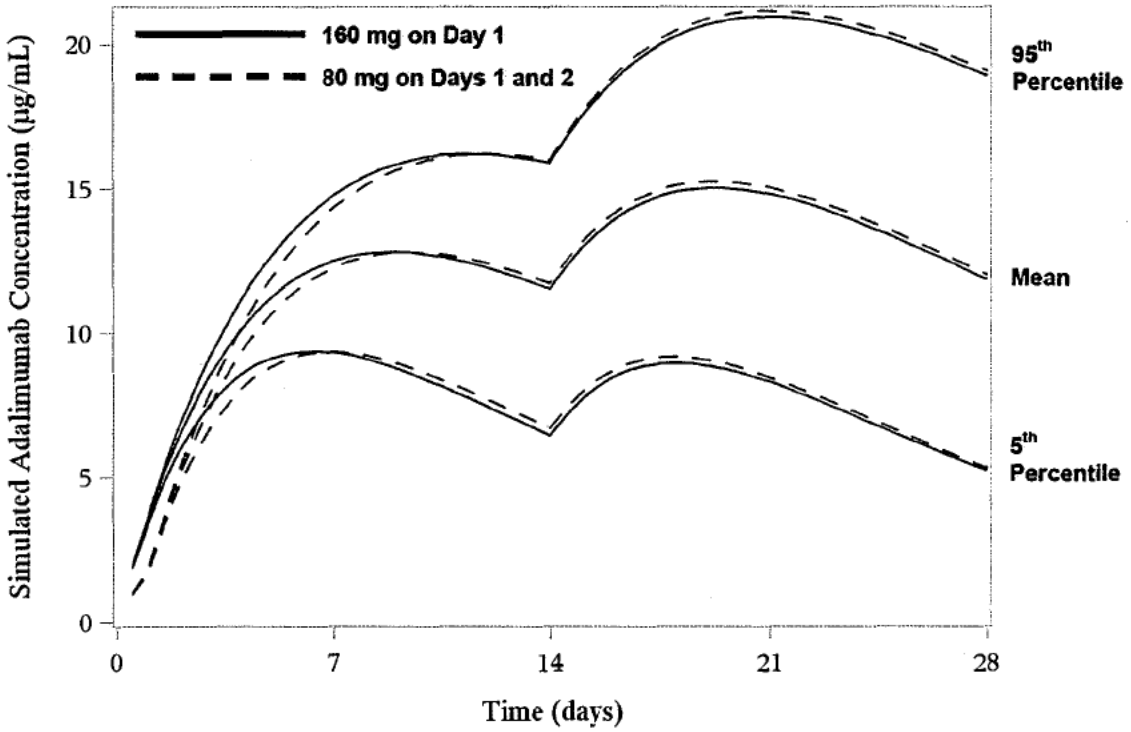
The evaluation of dosing regimen was conducted based on three questions below.

1. Does the PK analysis support splitting the 160 mg induction dose (4 x 40 mg sc injections) into 80 mg (2 x 40 mg sc injections) per day for two consecutive days?

   Yes, splitting the induction dose of 160 mg into two 80 mg doses administered over two days will not result in any meaningful differences in exposure to adalimumab. Figure 3 shows the simulated mean concentration-time profile for the standard and alternative split induction dosing regimens using the individual PK parameter estimates from the sponsor's final population PK model. It is worth noting that splitting 160 mg dose into two 80 mg dosing on two consecutive days is approved for adalimumab in Crohn's Disease indication based on support from model-based analysis.

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Figure 3. Adalimumab PK profiles comparing the two induction dosing regimens: 160 mg administered on day 1 or 80 mg administered on Day 1 and 2. Both regimens receive an additional 80 mg dose on day 14.



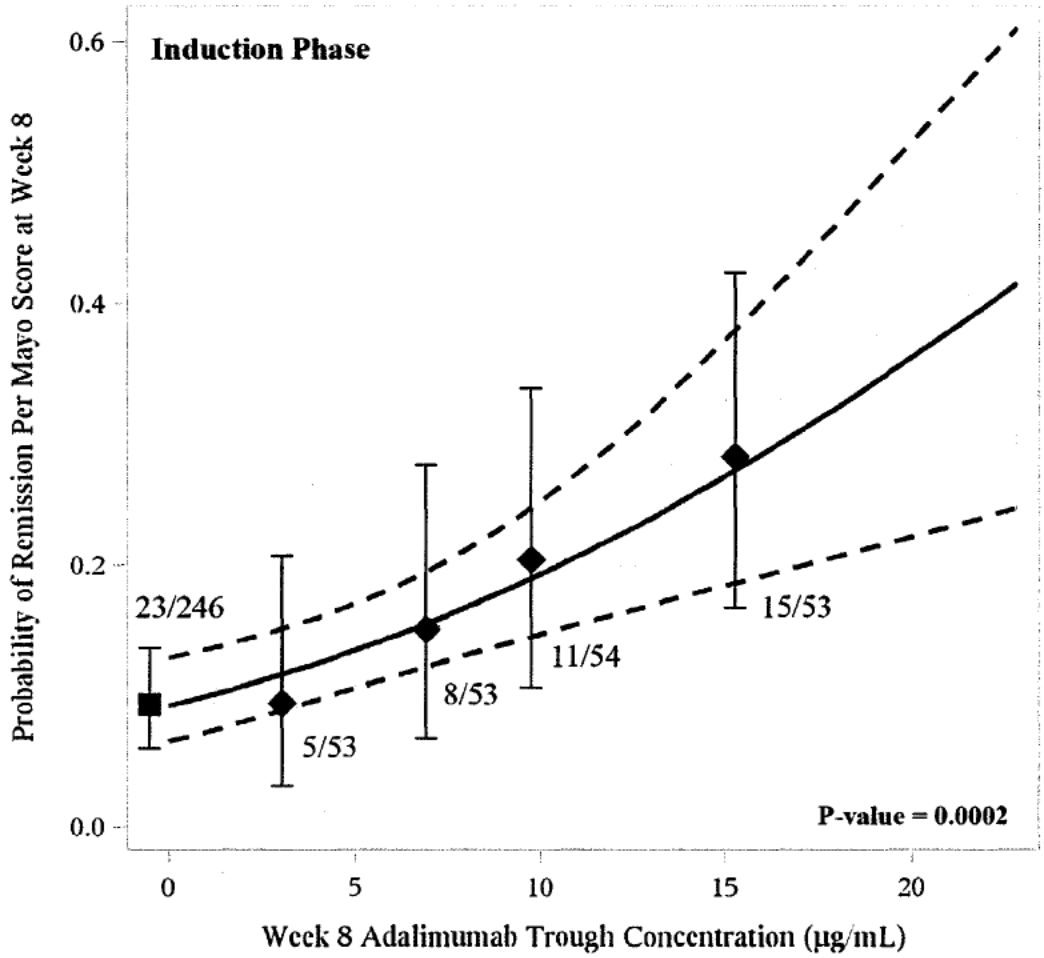
2. Does the exposure-response relationship for clinical remission at week 8 support the proposed dosing regimen for the induction phase?

   No. The exposure-response relationship for clinical remission at week 8 indicates that the dose range for inducing remission has not been fully explored. This conclusion is derived mainly from two observations. First, there was an increased remission rate with increased exposures that did not plateau at higher exposures. Second, patients with lower exposures in the induction phase were unable to maintain response and switched to open label treatment earlier than patients with higher exposures. These data suggest that the induction dose studied in the phase 3 program is not optimal and a higher dose for induction may provide better efficacy.

   A statistically-significant (p=0.0002) relationship was established between adalimumab week 8 trough concentration and clinical remission at week 8 (induction phase) using logistic regression. Figure 4 demonstrates the exposure-response relationship for clinical remission per Mayo score at week 8 depicting that higher exposures may be associated with higher remission rate. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Sponsor has not tested a dosing regimen higher than 160/80/40 in their clinical development program. The rate of clinical remission for the adalimumab 160/80/40 arm in the study M06-826 was 18.5% versus 9.2% in the placebo group, p=0.031 while study M06-827 had clinical remission rate of 16.5% for adalimumab 160/80/40 versus 9.3% in the placebo group, p=0.019.

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Figure 4. Probability of remission at week 8 increases with increasing week 8 adalimumab trough concentrations. Logistic regression model of the probability of remission per Mayo score at week 8 as a function of week 8 adalimumab trough concentrations.



Logistic regression modeling was also performed using numerous risk factors including baseline mayo score, prior anti-TNF exposure, age, corticosteroid use, immunomodulator use etc. Baseline Mayo score ($p<0.0001$) and prior exposure to anti-TNF therapy ($p=0.022$) were the only risk factors which demonstrated a statistically significant relationship to week 8 remission using univariate logistic regression analysis. Patients with higher baseline mayo score and prior anti-TNF exposure had lower remission rate. Multivariate logistic regression was performed to determine if the relationship between week 8 adalimumab trough concentration and week 8 remission was confounded by baseline mayo score and prior anti-TNF exposure. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant ($p=0.0003$).

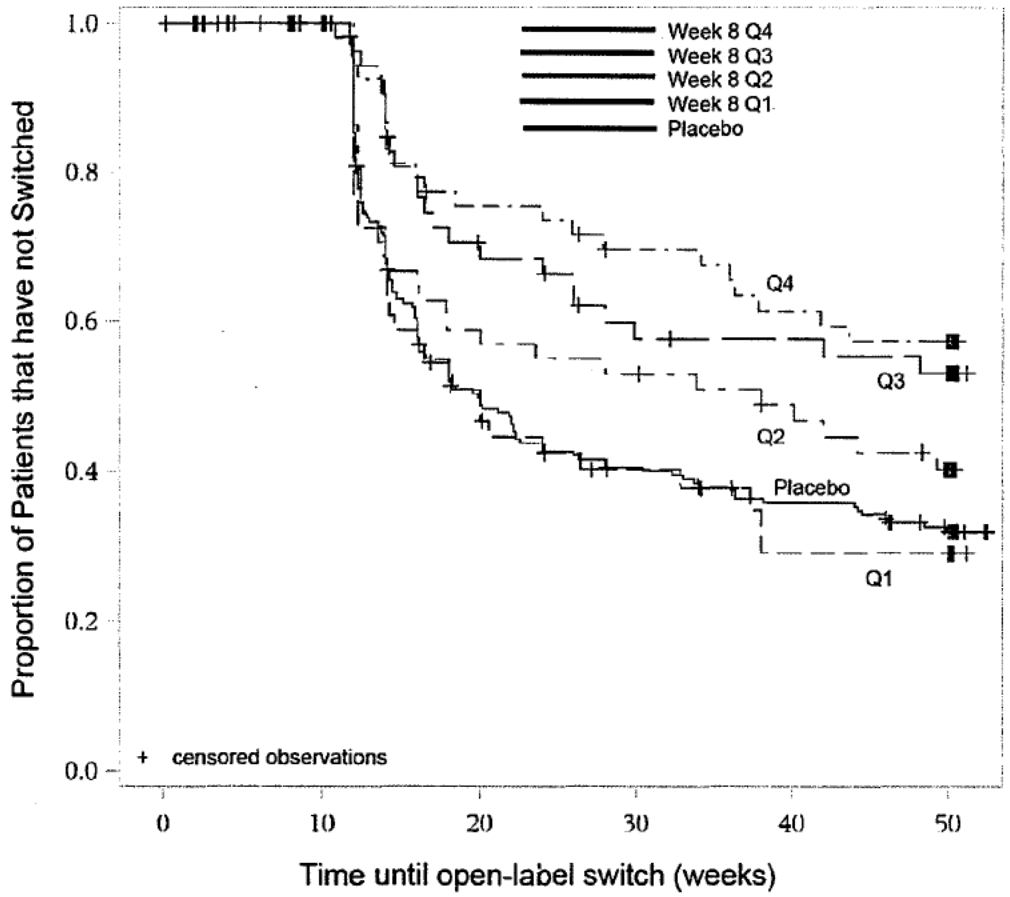
Subjects who exhibited inadequate response during the maintenance phase were able to switch from their double-blind treatment assignment to open-label adalimumab 40 mg every other week (eow) starting at week 12. Kaplan Meier analysis was conducted to explore the relationship between week 8 concentrations and time to open-label switch. Individuals were

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first grouped into 4 quartiles based on the Week 8 adalimumab trough concentration data. The proportion of subjects who switched to open-label adalimumab eow treatment in each quartile group was plotted over time to examine if an increase in concentration is associated with an increase in time to open-label switch.

Figure 5 demonstrates that subjects who had lower week 8 adalimumab trough concentrations exhibited inadequate response earlier than the subjects with higher week 8 concentrations. This provides additional evidence that exposures achieved by 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy and baseline mayo score.

Figure 5. Low Week 8 adalimumab concentration quartiles are associated with time to open label switch due to inadequate response. Kaplan-Meier plot of the proportion of subjects who have not switched vs. week 8 adalimumab trough concentration quartile. Patients who did not switch to open label were censored and are indicated by the "+" symbol.

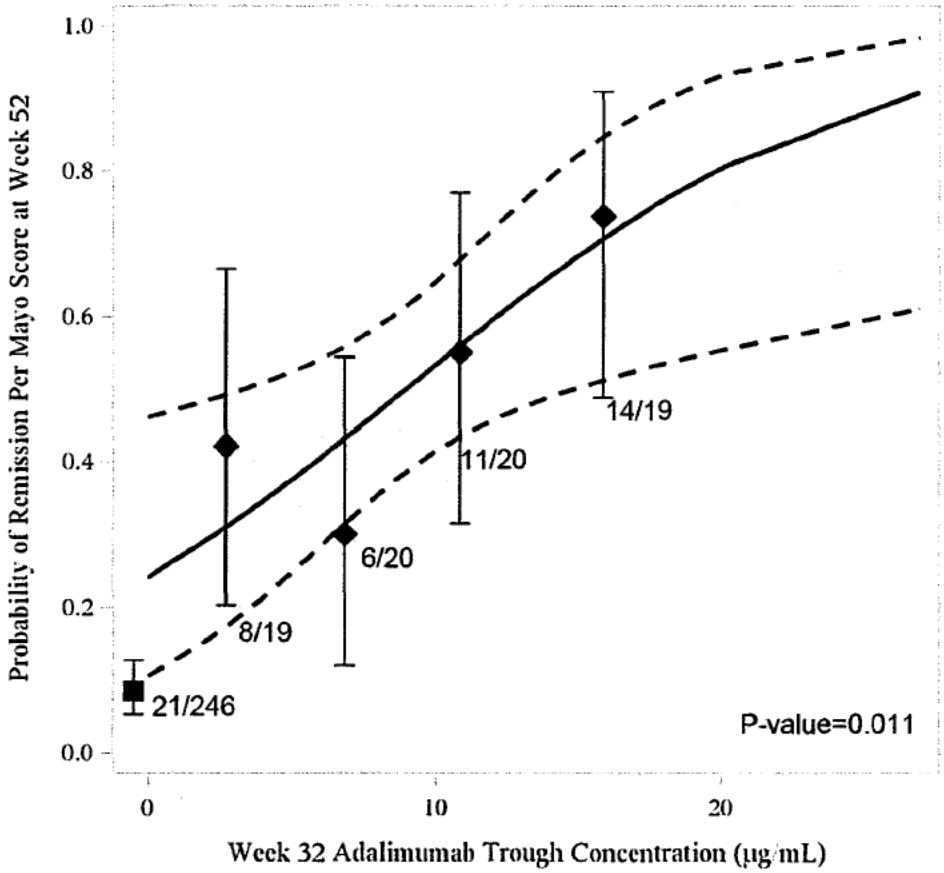


3. Does the exposure-response relationship for clinical remission at week 52 support the proposed dosing regiment for the maintenance phase?

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A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Two limitations of the exposure-response are (1) the analysis was based on only 78 patients (31% of the total treatment population) who remained in double-blind phase throughout the trial and had PK data and (2) the analysis dataset included non-responders (i.e., non-remitters) at week 8. Furthermore, only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline mayo score and prior anti-TNF use. While dose escalation was allowed in the trial, the study design does not permit evaluation of the effect of dose escalation on efficacy.

Figure 6. Probability of remission at week 52 increases with increasing week 32 adalimumab trough concentrations. Logistic regression model of the probability of remission per Mayo score at week 52 as a function of week 32 adalimumab trough concentrations.



2.2.5 What are the PK characteristics of the drug?

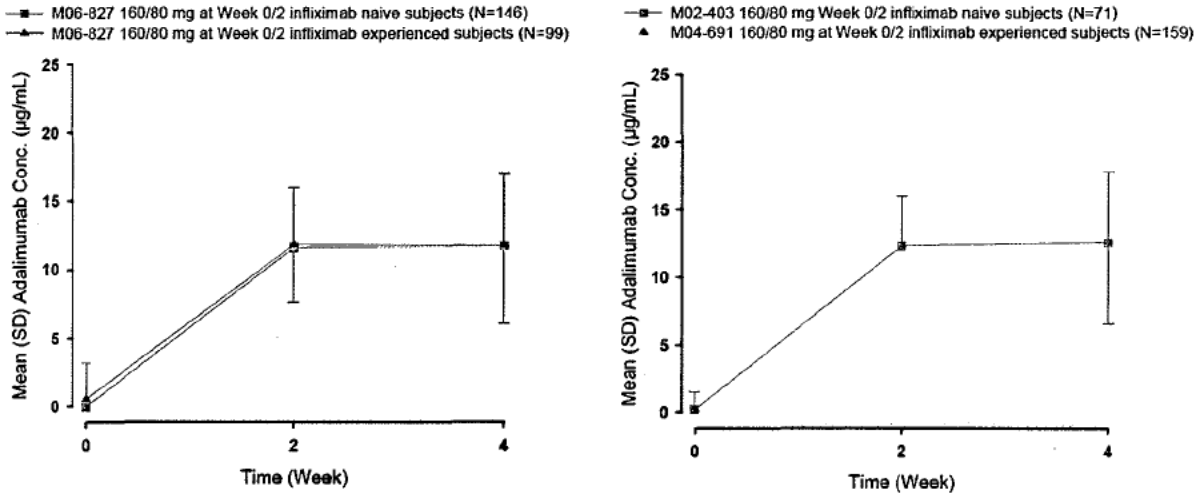
Induction Regimen

The sponsor evaluated the PK of adalimumab during the induction period in 245 subjects with moderately to severely active UC (Study M06-827 PK Report). These PK data were compared to PK data in subjects with moderately to severely active CD. The PK data in CD subjects were previously submitted with the CD indication extension application and included 159 subjects who had previously responded to infliximab but stopped responding or were intolerant to infliximab (Study M04-691 PK Report R&D/06/114) and 71 infliximab-naïve CD subjects (Study M02-403 PK Report R&D/03/819).

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The mean concentrations of adalimumab at week 4 were similar between UC subjects (11.7 µg/mL) and CD subjects (infliximab intolerant or naïve) (12.6 µg/mL) following the induction dose of 160 mg/80 mg administered at Week 0/Week 2 (Figure 7).

Figure 7. Serum Adalimumab Concentrations During Induction Period (at Week 4) in Subjects with UC (Study M06-827) and Subjects with Crohn's Disease (Study M02-403 and Study M04-691) (Source: Module 2.5 Clinical Overview, page 12/50)



Maintenance Regimen

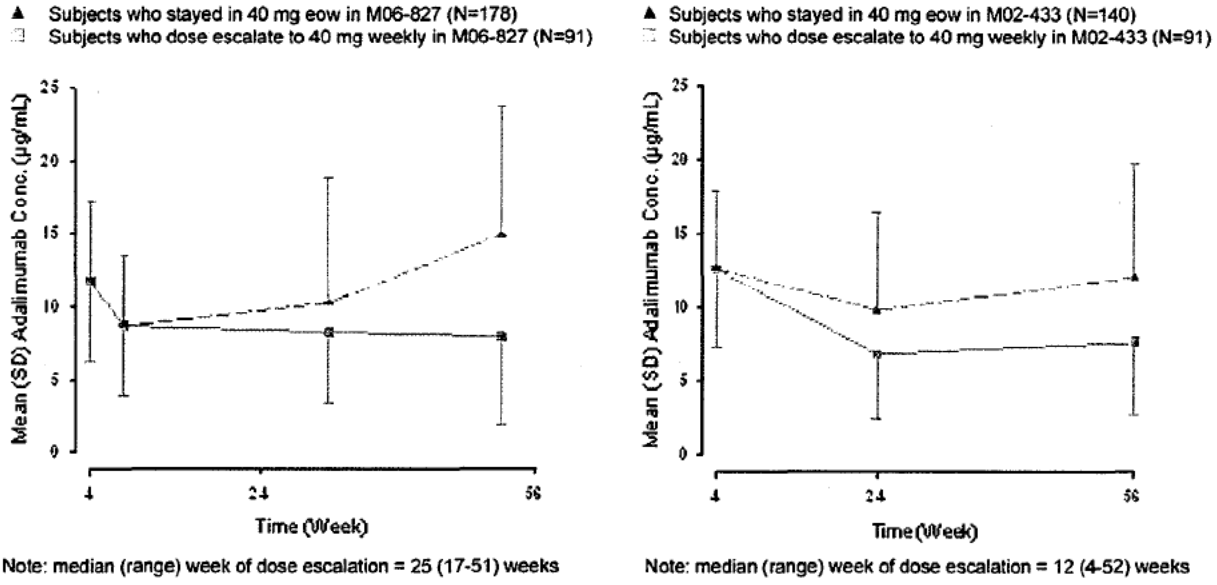
The sponsor evaluated the PK of adalimumab during the maintenance period in 245 subjects with moderately to severely active UC (Study M06-827 PK Report). These PK data were compared to PK data in 231 subjects with moderately to severely active CD during a 56-week maintenance regimen (Study M02-433 PK Report R&D/05/187).

Following the maintenance treatment at 40 mg eow, serum concentrations (mean ± SD) of adalimumab were consistent between subjects with UC (7.97 ± 6.09 µg/mL at Week 52, Study M06-827 PK Report) and subjects with CD (7.22 ± 4.58 µg/mL at Week 56, Study M02-433 PK Report R&D/05/187). Comparative plots are shown in Figure 8.

In addition, in subjects with UC (Study M06-827), the adalimumab concentrations at Week 52 were approximately double (15.0 ± 8.75 µg/mL) in subjects who dose escalated to 40 mg weekly compared to those who received 40mg eow. Same trend was observed in subjects with CD (Study M02-433).

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Figure 8. Comparison of Serum Adalimumab Concentrations Following 40 mg eow or 40 mg ew Maintenance Treatment in Subjects with UC (Study M06-827) and Subjects with Crohn's Disease (Study M02-433)
(Source: Module 2.5 Clinical Overview, page 13/50)



2.3 Intrinsic Factors

2.3.1 Effect of body-weight and plasma albumin concentration
Population PK analysis shows that body weight and plasma albumin concentration are statistically significant covariate on the apparent clearance of adalimumab, however the effect of these covariates is not considered to be clinically relevant. No dosage adjustment based on these covariates is warranted. Please see the appended pharmacometric review (page 9) for details.

2.3.2 Immunogenicity
The impact of immunogenicity on pharmacokinetics of adalimumab cannot be evaluated because the dataset is limited due to the inadequacy in the assessment of immunogenicity incidence. For more information please see Section 2.6. No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety.

2.4 Extrinsic Factors

2.4.1 Effect of prior anti-TNF therapy
Prior anti-TNF therapy does not appear to have an effect on the PK of adalimumab in Study 06-827 up to week 8. As shown in Table 3, for the first 8 weeks, the mean adalimumab trough concentrations were similar in anti-TNF-naïve and anti-TNF-experienced subjects who were assigned to the double-blind 160/80/40mg eow treatment group.

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Table 3. Summary of Adalimumab Concentrations versus Time (First 8 Weeks) for Subjects in the Double-Blind 160/80/40 mg eow Treatment Group by Previous Anti-TNF Treatment Status (Source: Module 5.3.5.1.1 Study M06-827_PK Report, page 59 of 1765)

Double-Blind 160/80/40 mg eow Treatment (N = 245)	**Mean ± SD (Min – Max), N_{nmiss}**			
	Week			
	0	**2**	**4**	**8**
Subjects with Previous Anti-TNF Treatment (N = 110)[a,b,c]	0.479 ± 2.51 (0.000 – 18.8), 103	11.5 ± 4.32 (0.000 – 25.7), 106	11.6 ± 5.51 (0.000 – 26.2), 97	8.18 ± 4.87 (0.000 – 22.8), 91
Subjects without Previous Anti-TNF Treatment (N = 135)[d]	0.000 ± 0.000 (0.000 – 0.000), 125	11.8 ± 3.86 (0.000 – 23.1), 127	11.9 ± 5.52 (0.000 – 25.6), 127	9.05 ± 4.75 (0.000 – 19.6), 124
All Subjects (N = 245)	0.216 ± 1.70 (0.000 – 18.8), 228	11.7 ± 4.07 (0.000 – 25.7), 233	11.7 ± 5.50 (0.000 – 26.2), 224	8.68 ± 4.81 (0.000 – 22.8), 215

N_{nmiss} = number of non-missing observations

a. Subjects 71301 and 78606 were included as previous anti-TNF treated due to their measurable infliximab concentration at Baseline even though they were anti-TNF -naïve in clinical database.

b. Eleven subjects (72903, 74501, 74507, 78601, 78907, 81004, 81007, 82003, 84115, 85201 and 85402) were included as anti-TNF experienced due to their measurable HACA results at Baseline even though they were anti-TNF naïve in clinical data base.

c. Ten subjects were included as previous anti-TNF treated per the clinical database but have no samples collected for infliximab or HACA assay to confirm.

d. Eleven subjects were included as previous anti-TNF naive per the clinical database but have no samples collected for infliximab or HACA assay to confirm.

Cross reference: Table 14.2__1

2.4.2 Effect of baseline HACA status

Patients who were exposed to infliximab are likely to develop HACA. The impact of HACA on the PK of adalimumab is not clear because **the sponsor's analysis is flawed.**

Adalimumab trough concentrations tended to be lower in HACA+ subjects than in HACA- subjects for the double-blind 160/80/40 mg treatment group who continued on 40 eow (Figure 9, left panel). For subjects in the double-blind 160/80/40 mg treatment group who dose-escalated to 40 mg weekly **(Figure 9, right panel), the sponsor's analysis is** confounded by the time of dose escalation, i.e. subjects were dose-escalated at different time points and not everyone in the plot reached steady state at week 32 or 52. Therefore, the comparison of week 32 and week 52 adalimumab trough concentrations in subjects as presented in the right panel of Figure 9 is not appropriate. As such the presence or absence of a difference can not be concluded in this subgroup.

For the same reason, the differences in adalimumab concentration between HACA+ and HACA- subjects for the placebo group (Figure 10, both panels) were inconclusive.

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Figure 9. Individual and Median Adalimumab Concentrations versus Time by HACA Status at Baseline for Double-Blind 160/80/40 mg eow Treatment Group
(Source: Module 5.3.5.1.1 Study M06-827_PK Report, page 61 of 1765)

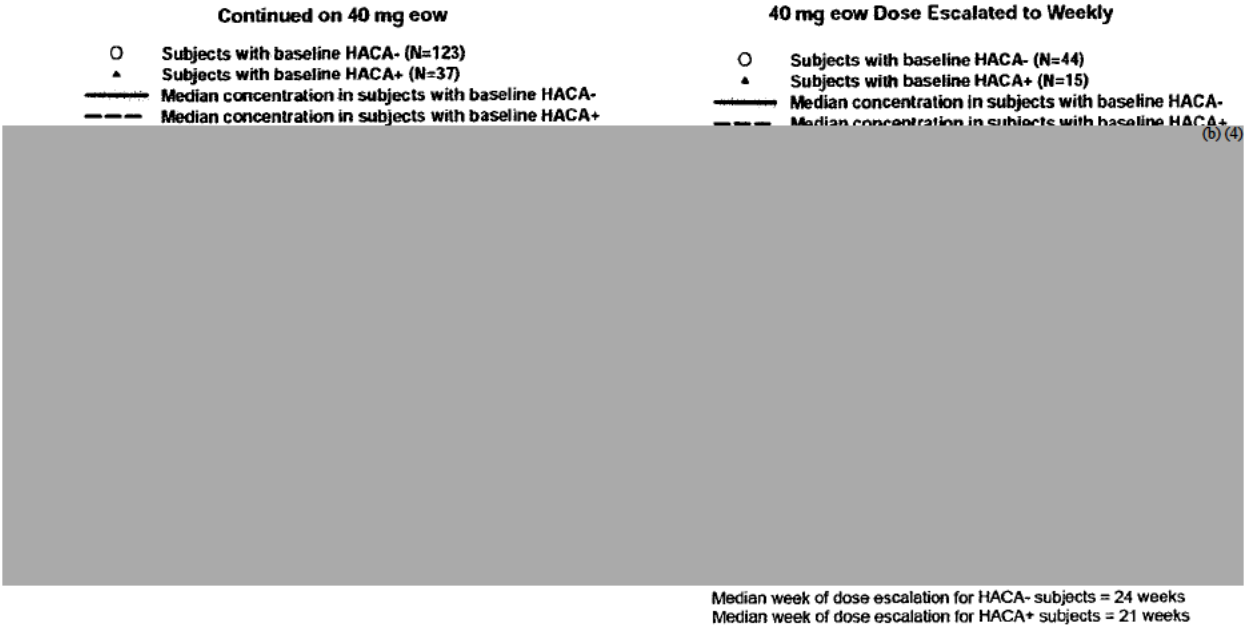
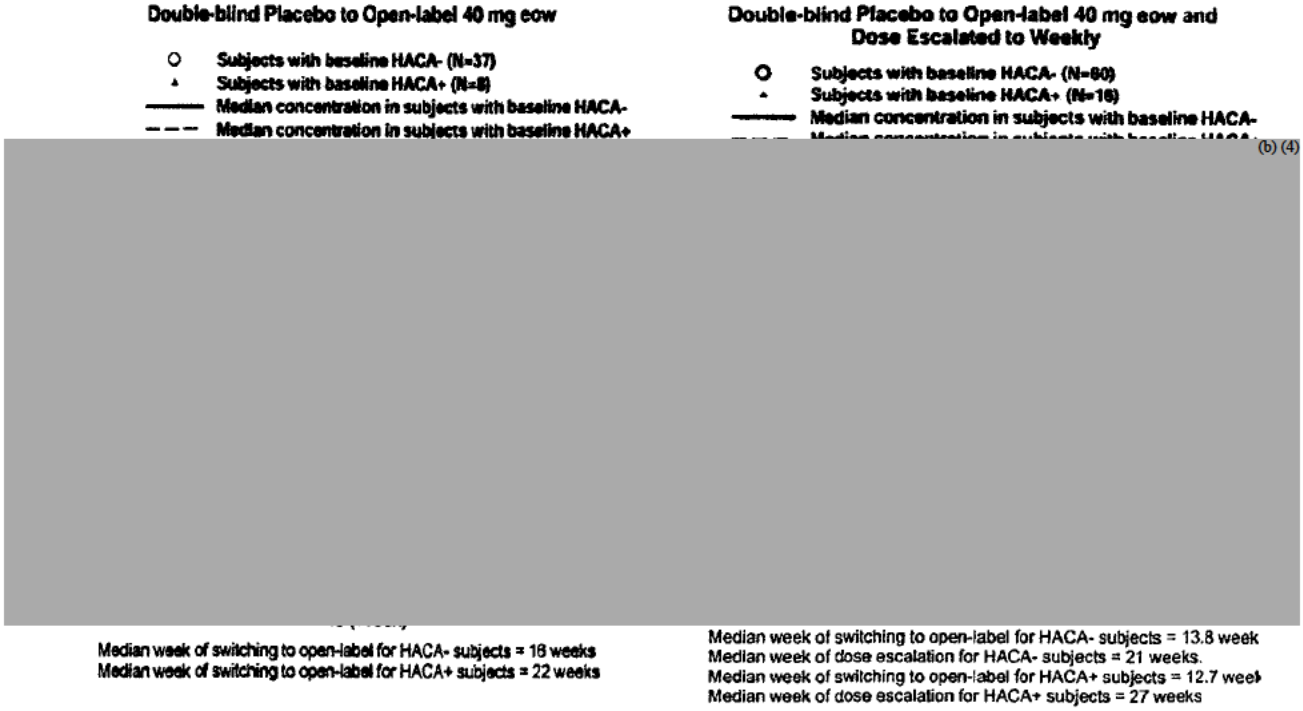


Figure 10. Individual and Median Adalimumab Concentrations versus Time by HACA Status at Baseline for Double-Blind Placebo Treatment Group
(Source: Module 5.3.5.1.1 Study M06-827_PK Report, page 62 of 1765)



2.4.2 Effect of concomitant therapy
In Study M06-827, subjects were allowed to take UC specific concomitant medications, including immunosuppressants (aminosalicylates, azathioprine, 6-MP or methotrexate), oral corticosteroids (prednisone or equivalent) and probiotics.

Subjects were not allowed to change the dosage of UC specific concomitant medications throughout the study with the following exceptions: 1) decrease corticosteroid dose between Weeks 8 and 52; and 2) a dose decrease of other UC-related concomitant treatments in the event of UC treatment-related toxicities (e.g., leukopenia or elevated liver enzymes) considered moderate to severe in the opinion of the investigator.

Population PK analyses were performed in NONMEM to estimate the apparent clearance and apparent volume of distribution of central compartment and volume of distribution of the peripheral compartment of adalimumab in subjects with UC. The structure of the starting pharmacokinetic model was based on observations from a population pharmacokinetic analysis performed with data collected from studies with adult rheumatoid arthritis subjects. Based on the PopPK analysis, the concomitant immunosuppressants was not a significant covariate on the apparent clearance of adalimumab.

2.4.3 Potential for DDI
Adalimumab is a known modulator of cytokines (e.g., IL-6 and TNF-α). These cytokines are known to modulate cytochrome P450 (CYP) activity in humans and alter the metabolism of CYP substrates [1,

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2]. Patients with inflammatory diseases have elevated cytokines levels and suppressed CYP enzyme activity [3]. After treatment of adalimumab the cytokine levels decreases in these patients which may restore CYP activities to higher levels leading to increased metabolism of drugs that are CYP substrates.

The following request was sent to the sponsor in an information request letter dated 09/222011 as the current adalimumab labeling does not reflect such DDI potential.

"Please update the adalimumab labeling Section 7.1 Drug interactions and Section 12.3 Pharmacokinetics to reflect that treatment with adalimumab can have impact on CYP enzymes and the potential of drug-drug interaction (DDI) between adalimumab and CYP substrates. Additionally, we recommend that you develop a strategy to quantitatively evaluate potential DDI which may include **conducting prospective clinical studies."**

Sponsor's Response (submitted on 10/12/2011):
"In response to the Agency's request, the draft labeling has been updated as follows.

7.4 Cytochrome P450 Substrates
The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. (b) (4) it is possible that for a molecule that antagonizes cytokine activity, such as adalimumab, the formation of CYP450 enzymes (b) (4) (b) (4) Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

12.3 Pharmacokinetics
(b) (4)

Abbott will address the Agency's request to develop a strategy to quantitatively evaluate potential DDIs. If further studies are required, Abbott w**ill discuss these in detail with the Agency."**

2.5 Analytical Section

2.5.1 Adalimumab concentration determination
A total of 2616 serum samples from 487 subjection in Study M06-827 were analyzed at Abbott GmbH & Co. (Knollstrasse 50, D-67061 Ludwigshafen, Germany) between 13 May 2009 and 28 April 2010. All samples were analyzed using the final analytical method described in the validation report ANA09-004: Determination of Adalimumab in Human serum via Double-Antigen- Bridging-ELISA (b) (4)) R&D09/341.

2.5.1.1 PK sample collection schedule
For adalimumab assay, all samples were obtained immediately prior to dosing at Weeks 0 (Baseline), 2, 4, 8, 32 and 52 or Early Termination Visits.

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2.5.1.2 What bioanalytical methods were used to assess the concentrations of adalimumab in serum?
The analytical method for adalimumab is summarized in Table 4 below.
Serum concentrations of adalimumab were assayed using a sandwich ELISA (double antigen technique). Features of the assay are listed in table 4 below.

Table 4. ELISA Conditions of Analytical Method for Adalimumab
(Source: Module 5.3.5.1.1 Study M06-827_PK Report, page 277 of 1765)

Assay range	**3.13 to 50.0 ng/mL diluted serum**
Calibration Standards	**1.25*, 2.5*, 3.13, 5.00, 7.5, 10.0, 20.0, 30.0, 40.0, 50.0, 100.0*, 200.0* ng/mL Adalimumab**
Limit of quantitation	**3.13 ng/mL diluted serum**
Sample volume	**100 µL diluted serum (≥ 1:10)**
Coating	**Streptavidin – recombinant human TNF-α^{biotin}**
Detection	**Recombinant human TNF-α-POD conjugate at 450 nm**
Data processing	**GDA Bioanalytical LIMS v2 using 5PL (Marquardt) Model with 1/Y weighting**
Specificity	**The double antigen sandwich ELISA determines both, the complete antibody as well as the $F(ab)_2$-, but not F_{ab}-fragment. The assay only detects Adalimumab capable of bridging two TNF-α molecules. Adalimumab complexed with TNF-α or neutralizing anti-Adalimumab antibodies will not be detected.**

***Anchor Calibrators**

2.5.1.3 What are the lower and upper limits of quantification (LLOQ/ULOQ)?
The assay range was from 3.125 ng/mL to 50.0 ng/mL in diluted serum.

2.5.1.4 Is the assay methods adequately validated?
The assay method is adequately validated from a clinical pharmacology perspective.

All samples were analyzed using the final analytical method described in the validation report ANA09-004: Determination of Adalimumab in Human serum via Double-Antigen- Bridging-ELISA (b) (4) (b) (4) (b) (4) R&D09/341. This analytical method is based on the original analytical **method in R&D /01/819, entitled "Determination** of Adalimumab is Human Serum via Sandwich **ELISA (Double Antigen technique)." The valid**ation report for R&D/01/819 was submitted in the original BLA 125057 (Jacket 36, volume 1, page 256).

According to the sponsor, there are only minor modifications between these two analytical methods to fulfill current assay requirements which include (b) (4) (b) (4) The general assay principle (Double-antigen Sandwich ELISA) was not changed.

Validation report ANA09-004 is a (b) (4) performed (b) (4) r and slight modification of the validated method provided by (b) (4), Determination of Adalimumab (LU200134)(D2E7) in Human Serum by ELISA - (b) (4) ANA09-001, R&D/09/190, (b) (4). In order to prove that the method is robust, reliable, and (b) (4) (b) (4), intra- and interassay precision and accuracy experiments were performed, as well as the determination of the Adalimumab concentration in samples which had been analysed by (b) (4)

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[redacted] (b) (4) before.

1. Evaluation of Linearity of Calibration Standard Curve:
   Evaluation of the linearity of the calibration standard curve was performed including all thirteen accepted validation runs. (Source: Serial # 97 dated 10/07/2011, Module 5.3.1.4.1 Study M06-827_PK Report, page 211 of 344)

Acceptance Criteria	Method of Computation	Results
At least ¾ of the calibration standards within the assay range must meet the following criteria: %CV (raw data) <= 20 %Bias within ± 25	Performed Five-Parameter Logistic Model (Marquardt) with 1/Y weighting using calibration standard curve points. Deviation from the nominal concentration was computed using the final fitted equation	%CV < 6.5 %Bias 1.7-4.5
Coefficient of determination r^2 >= 0.9025	r^2 was computed using GDA Bioanalytical LIMS V2	r^2 >=0.99

2. Evaluation of QC samples
   QC performance was evaluated including all twelve accepted validation runs. (Source: Serial # 97 dated 10/07/2011, 5.3.1.4.1 Study M06-827_PK Report, page 212 of 344)

Acceptance Criteria	Method of Computation	Results
At least 2/3 (4 out of 6) QC duplicates level have to meet the following criteria and each concentration level is covered by at least one QC-duplicate: %CV for each duplicate must be <= 20	%CV was computed using the calculated concentration from all validation batches	Inter-Assay %CV LQC: 6.7 MQC: 5.2 HQC: 10.1
%Bias of the QC-duplicate must be within ± 25	Mean Bias was computed using the calculated concentrations and the nominal concentration from all validation batches	Inter-Assay %Bias LQC: (-4.8) MQC: (-5.0) HQC: (-1.6)

3. Evaluation of the Intra-and Inter-assay Precision and Accuracy (ANOVA) of Analytical Performance Evaluation (APQC) Samples
   Intra- and Interassay precision and accuracy were evaluated including six accepted validation runs. (Source: Serial # 97 dated 10/07/2011, 5.3.1.4.1 Study M06-827_PK Report, page 213-4 of 344)

Acceptance Criteria	Method of Computation	Results
Relative %Bias must be within ± 25	Concentrations of the evaluation samples were back calculated from the calibration curve. Intra-assay precision and accuracy (ANOVA) was calculated using GDA Bioanalytical LIMS V2	%Bias -0.5 to -9.2
%CV must be <= 20		Within Run Precision %CV: **2.9 – 8.2** Between Run Precision %CV:

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		4.0 – 7.8 Total Variation %CV: **4.9 –11.1**
Total Error must be <35%	Total error was calculated by the addition of l%Biasl + Total Variation %CV	% Total Error: **5.4 – 20.3**

4. Determination of the Adalimumab concentration of 30 study samples- (b) (4) to previous results by (b) (4)
   Thirty individual specimens were analysed for their Adalimumab content in seven accepted validation runs. Three of the samples had to be re-analysed due to failure of dilution linearity criteria.

Acceptance Criteria	Method of Computation	Results
At least 2/3 of the results have to fulfill the following criteria: **l(determined result – original** result from (b) (4))/Mean Valuel * 100% < 30%	Concentrations of the evaluation samples were back calculated from the calibration curve. For further calculations Excel 2003 was used.	20 out of 30 samples fulfill the acceptance criteria

2.5.2 Anti-Adalimumab antibody (AAA) status determination

2.5.2.1 AAA sample collection schedule
Immunogenicity of adalimumab in subjects with UC was assessed in 360 subjects in Study M06-827. For AAA assay, all samples were obtained immediately prior to dosing at Weeks 0 (Baseline), 8, 32 and 52 or Early Termination Visits.

2.5.2.2 What bioanalytical methods were used to assess the antibody formation against adalimumab in serum?
The AAA assay was a validated ELISA method based on a double-antigen technique. The LLOQ for AAA was established at 0.5 ng/mL in diluted serum. The assay method is reviewed by CMC reviewer Dr. Jun Park.

2.5.2.3 Is the assay methods adequately validated?
According to the CMC's Review, the validation of the assay was acceptable.

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2.5.2.4 What is the strategy for AAA sample analysis?
The sponsor first determined the adalimumab concentration in the serum samples. Then, AAA assay was conduct on samples with serum adalimumab concentrations less than 2 µg/mL whereas **serum samples with adalimumab concentrations >= 2 µg/mL were not analyzed for AAA.** The sponsor provided the following rationale for the strategy. The assay detects free (unbound) AAA. Adalimumab present in the sample complexes AAA and prevents it from binding simultaneously to the capture- and detector-adalimumab used in the AAA assay. Samples containing adalimumab concentration >= 2 µg/mL may result in negative or borderline AAA results.

2.5.2.5 What are the criteria for AAA data interpretation?
Serum samples were considered to be positive for AAA (AAA+) if both of the following criteria were met:
1) The measured AAA concentration was greater than 20 ng/mL;
2) The serum sample was collected within 30 days after an adalimumab dose.

Sponsor's rationale for each of the criteria:

1) In the validated assay, a cut-off of 20 ng/mL of AAA allowed for the detection of a false positive rate of 5%;
2) The criterion of serum samples having to be collected within 30 days of a subject's previous dose is used to detect the presence of potentially clinically meaningful AAA in subjects who are on active adalimumab treatment. The proposed dosing regimen for UC is 40 mg adalimumab eow and therefore AAA detected beyond 30 days represents immunogenicity developed while off treatment, thus would not be impactful.

Reviewer's comment on sponsor's rationale:
The first criterion is reasonable. For the second **criteria, however, the Sponsor's statement "AAA** detected beyond 30 days represents immunogenicity **developed while off treatment" is not valid.** Antibody developed during treatment may not have been detected within 30 days post-treatment if the samples were not analyzed for AAA according to the strategy described above (section 2.5.3). Due to the limitation of the assay, a subject who developed AAA during treatment could have been labeled as AAA negative because the serum samples had adalimumab concentration no less than 2 µg/mL and were not assayed for AAA. As such, the AAA detected beyond 30 days does not necessarily represent immunogenicity developed while off treatment.

2.6 Immunogenicity Section

2.6.1 What is the AAA-positive rate?
In the original sBLA submission, the sponsor reported that, in Study 827, the overall AAA-positive rate was 3.9% (19/487). The clinical pharmacology team believes that this estimated rate very likely under-estimates the true immunogenicity rate because the denominator the sponsor used in the calculation is not appropriate. The reviewer had significant comments **about the sponsor's assessment** with respect to the estimation of immunogenicity incidence rate. These comments were communicated to the sponsor through two information requests, dated 07/11/11 and 09/22/11.

In response to the Agency's request, the sponsor recalculated the immunogenicity rate using two methods; 1) using all subjects who have received adalimumab in Study M06-827 and have evaluable

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immunogenicity data regardless of adalimumab serum concentration (N = 360) as the denominator. 2) using the number of all subjects who received adalimumab in Study M06-827, and have evaluable immunogenicity data and have serum concentrations below 2 µg/mL as the denominator (N = 92). Calculations using both methods are presented in Table 5 below.

Table 5. **AAA+ Rate for Subjects in Study M06-827**
(Source: Sponsor's submission dated 10/12/2011, Serial # 099)

Total No. Subjects with Eligible Immunogenicity Samples at any Time During the Study Regardless of Adalimumab Serum Concentration	**No. of Subjects with Eligible Immunogenicity Samples at any Time During the Study and have Adalimumab Serum Concentrations Below 2 mg/mL**	**No. of AAA+ Subjects**	**% of Subjects AAA+ Based upon all Subjects who have Eligible Immunogenicity Samples at any Time During the Study Regardless of Adalimumab Serum Concentration (N = 360)**	**% of Subjects AAA+ Based upon Subjects with Serum Adalimumab Concentrations Below 2 µg/mL (N = 92)**
360	92	19	5.3 %	20.7%

Based on these updated calculations, the sponsor proposed the following updates in the labeling,

"Section 6.1, 6.1 Clinical Trials Experience, (Immunogenicity) of the draft labeling has been updated as shown below. The format of this text is similar to that followed for immunogenicity for the psoriasis indication in the approved adalimumab label:

> In patients with moderately to severely active ulcerative colitis, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 ug/ml. Among the patients whose serum adalimumab levels were < 2 ug/ml (approximately 25% of total patients studied), the immunogenicity rate was **20.7%.**"

Reviewer's overall evaluation and recommendation:

The assessment of immunogenicity incidence was not adequate in the current submission. The majority of subjects (74.4%, 268/360) had no immunogenicity assessment due to high drug concentration (≥ 2 µg/mL) and they could not be ruled as negative. Among the subjects with immunogenicity assessed, anti-adalimumab antibodies (AAA) were observed in 20.7% (19/92) of patients treated with a maintenance dose of 40 mg eow or 40 mg ew through Week 52. In order to obtain an adequate adalimumab immunogenicity profile, we recommend that the Sponsor (1) develop an assay with improved drug tolerance to allow detecting anti-adalimumab antibodies in the presence of adalimumab drug concentration in the study samples collected from patients during treatment, and/or 2) collect post-dose samples at time points where the adalimumab drug concentrations are not expected to interfere with the immunogenicity assay (i.e., adalimumab concentration ≤ 2 µg/mL).

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2.6.2 What is the impact of immunogenicity on the adalimumab PK, efficacy and safety?
No conclusions can be made regarding the impact of immunogenicity on pharmacokinetics, clinical efficacy and safety because only very small proportion of subjects (about 26%) had confirmed antibody status. Out of 360 subjects who had eligible samples for immunogenicity samples, the number of subjects who were not tested for AAA status, who tested positive and who tested negative were, 268 (74.4%), 19 (5.3%), and 73 (20.3%)respectively.

3. DETAILED LABELING RECOMMENDATIONS
No detailed labeling recommendations.

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4. APPENDICES

4.1 Adalimumab Ulcerative Colitis Development Program Clinical Studies

(Source: Module 2.5 Clinical Overview, page 6)

Study No.	No. Patients Enrolled	Location/ Number of Centers	Study Design	Primary Objective	Status
M06-826	576	EU, US, CAN, PR/ 80	8- (or 12)-week randomized, double-blind, placebo-controlled period followed by open-label treatment through Week 52	To assess the efficacy and safety of 2 dosing regimens of adalimumab for the induction of clinical remission in subjects with moderately to severely active UC, and to assess maintenance of clinical remission during the open-label period of the study	Study completed
M06-827	518[a]	EU, US, CAN, AUST, NOR, NZ, ISR, SWI/ 103	52-week randomized, double-blind, placebo-controlled study	To assess the efficacy and safety of adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active UC	Study completed
M10-223	498[b]	EU, US, CAN, AUST, NZ, PR, SWI/ 120	Open-label extension study (up to 240 weeks)	To assess efficacy and safety of long-term use of adalimumab as maintenance therapy in subjects with ulcerative colitis who participated in and successfully completed Study M06-826 or Study M06-827	Study ongoing

AUST = Australia; CAN = Canada; EU = European Union; ISR = Israel; NOR = Norway; NZ = New Zealand; PR = Puerto Rico; SWI = Switzerland; US = United States

a. In Study M06-827, 517 subjects received study drug; 1 additional subject was randomized but did not receive study drug.

b. At the time of the data cut-off date for Study M10-223 (31 December 2009), 120 sites that enrolled subjects in Study M06-826 or Study M06-827 had enrolled 498 subjects in Study M10-223; additional sites enrolled subjects into Study M10-223 after that time point.

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4.2. Cover Sheet OCPB Filing/Review Form

Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA/BLA Number	125-057	Brand Name	Humira
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	Adalimumab
Medical Division	DGIP	Drug Class	Recombinant human IgG1
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)	Ulcerative Colitis
OCP Secondary Reviewer	Gilbert Burckart, PharmD	Dosage Form	PFS or pen
Pharmacometrics Reviewer	Lanyan Fang ?	Dosing Regimen	160 mg Day 1, 80 mg Day 15, followed by 40 mg every other week starting Day 29
Date of Submission	Jan 25, 2011	Route of Administration	S.C.
Estimated Due Date of OCP Review	8/25/2011	Sponsor	Abbott
Medical Division Due Date	9/25/2011	Priority Classification	Standard
PDUFA Due Date	11/25/2011	Dosing Strength	40 mg/vial

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

Reference ID: 3200370

Immunogenicity:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	4		**Pop PK and Trail simulation were used in the submission to support dosing regimen in the labeling**
Immunogenicity	X	3		**Assess impact of immunogenicity on efficacy and safety**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		16		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	How about post-marketing data?
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate	X			

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	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Covariate analysis in the popPK analysis
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

Fileable.

Lanyan Fang, Ph.D.

Clinical Pharmacology Reviewer Date

Gilbert Burckart, Pharm.D.

Acting Team Leader Date

Reference ID: 3200370

Filing Review Summary

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-dose, 1 mL prefilled glass syringe.

In December 2002, adalimumab was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) in the United States (US). On 27 February 2007, adalimumab was approved in the US for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Adalimumab has also been approved for indications in psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis.

The purpose of this submission is to submit an efficacy supplement for a new indication in adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The submission is based upon data from the following studies:

• **Study M06-826, entitled "A Multicenter, Randomi**zed, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

• **Study M06-827, entitled "A Multicenter, Randomi**zed, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

• **Interim results from Study M10-223, entitled "A Multicenter, Open-Label Study of the Human Anti-**TNF Monoclonal Antibody Adalimumab to Evaluate the Long Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects With Ulcerative Colitis"

The pharmacokinetics (PK) of adalimumab was evaluated in subjects with moderately to

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severely active ulcerative colitis (UC) in PK Study M06-827. The population pharmacokinetics of adalimumab was also evaluated for UC subjects using a non-linear mixed effects modeling (NONMEM) approach using data from PK Study M06-827. The impact of covariates on adalimumab pharmacokinetics was assessed.

The results (PK Study M06-827) were compared with results from previous studies in subjects with Crohn's disease (CD) in which subjects were administered a 4-week 160 mg/80 mg induction regimen (PK Study M02-403) and a 52-week 40 mg maintenance regimen (PK Study M02-433). The pharmacokinetics of adalimumab following a 4-week induction regimen were also evaluated in subjects with moderate to severe Crohn's disease who had lost response or were intolerant to infliximab in PK Study M04-691.

The immunogenicity of adalimumab was examined in all aforementioned studies (PK Study M06-827, PK Study M02-403, PK Study M02-433 and PK Study M04-691). The impact of immunogenicity on efficacy and safety were assessed.

Overall, the sBLA is filable from the clinical pharmacology standpoint. The clinical pharmacology review will review the comparison of adalimumab concentrations and immunogenicity results between UC and CD studies. A pharmacometric review which will focus on the popPK analysis and trial simulation for dosing regimen support in the labeling.

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4.3. Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	BLA 125057
Compound	HUMIRA (Adalimumab)
Submission Date	25 Jan 2011
Clinical Division	Gastroenterology Products
FDA Commissioner's Fellow	Michael Bewernitz, Ph.D.
PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm. D.

1 Summary of Findings

1.1 Key Review Questions

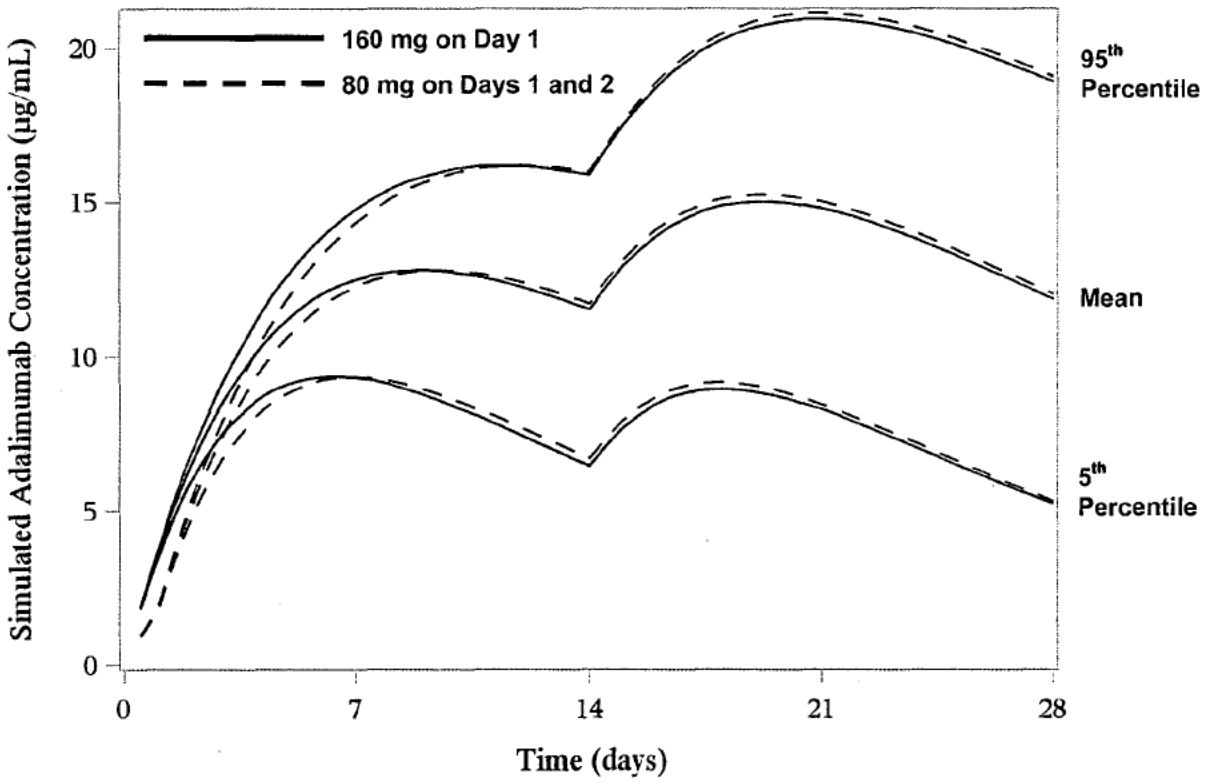
The purpose of this review is to address the following key questions.

1.1.1 Does the PK analysis support splitting the 160 mg induction dose (4 x 40 mg sc injections) into 80 mg (2 x 40 mg sc injectins) per day for two consecutive days?

Yes, splitting the induction dose of 160 mg into two 80 mg doses administered over two days will not result in any meaningful differences in exposure to adalimumab. Figure 1 shows the simulated mean concentration-time profile for the standard and alternative split induction dosing regimens using the individual PK parameter estimates from the sponsor's final population PK model. A similar strategy was used to approve an alternative split induction dosing regimen in the Crohn's Disease indication.

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Figure 1. Adalimumab PK profiles comparing the two induction dosing regimens: 160 mg administered on day 1 or 80 mg administered on Day 1 and 2. Both regimens receive an additional 80 mg dose on day 14.



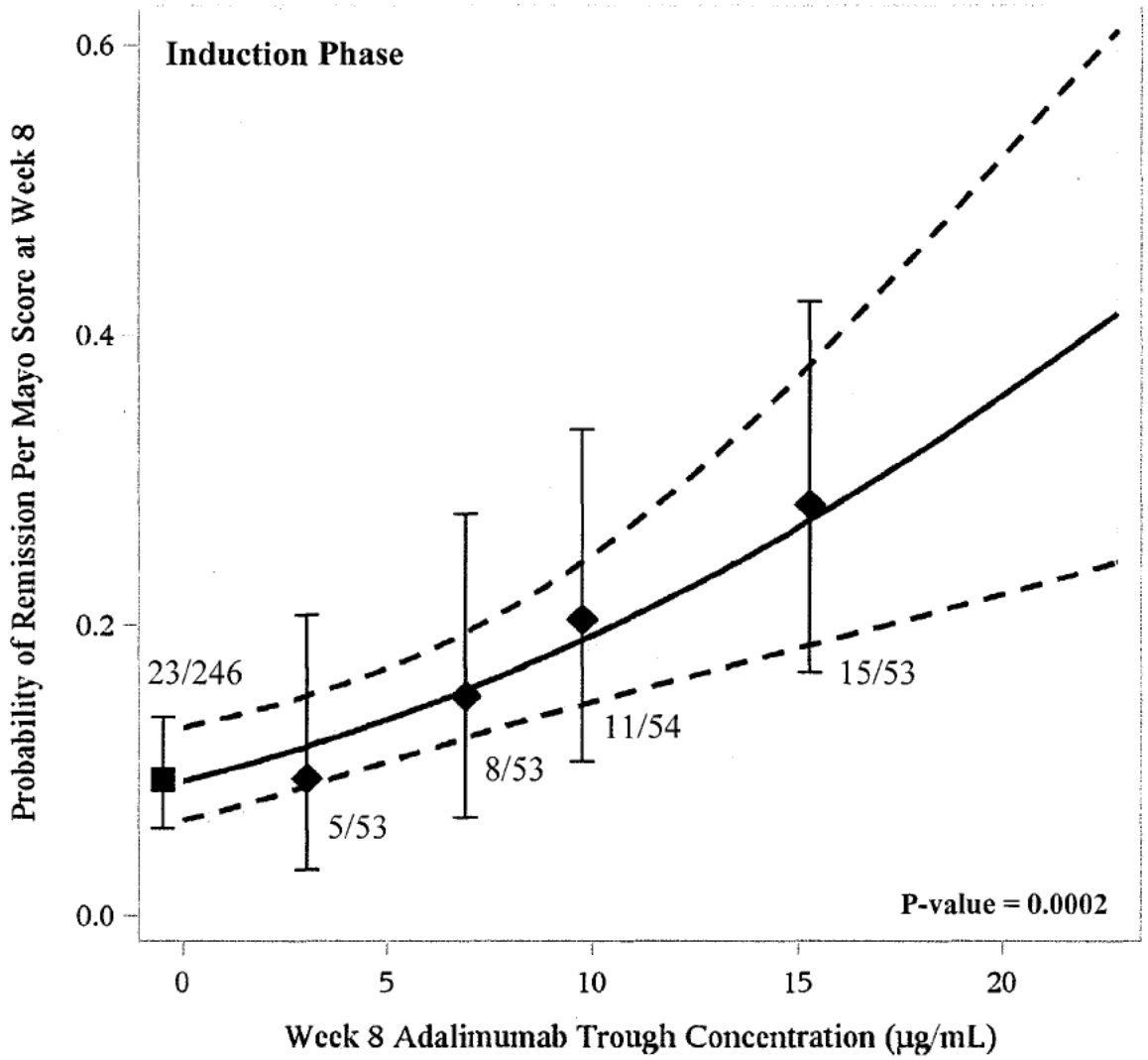
1.1.2 Does the exposure-response relationship for clinical remission at week 8 support the proposed dosing regimen for the induction phase?

No. The exposure-response relationship for clinical remission at week 8 indicates that the dose range for inducing remission has not been fully explored. This conclusion is derived mainly from two observations. First, there was an increased remission rate with increased exposures that did not plateau at higher exposures. Second, patients with lower exposures in the induction phase were unable to maintain response and switched to open label treatment earlier than patients with higher exposures. These data suggest that the induction dose studied in the phase 3 program is not optimal and a higher dose for induction may provide better efficacy.

A statistically-significant (p=0.0002) relationship was established between adalimumab week 8 trough concentration and clinical remission at week 8 (induction phase) using logistic regression. Figure 2 demonstrates the exposure response relationship for clinical remission per Mayo score at week depicting that higher exposures may be associated with higher efficacy. Thus, this finding suggests that a higher dose may produce additional benefit for inducing clinical remission. Sponsor has not tested a dosing regimen higher than 160/80/40 in their clinical development program. The rate of clinical remission for the adalimumab 160/80/40 arm in the study M06-826 was 18.5% versus 9.2% in the placebo group, p=0.031 while study M06-827 had clinical remission rate of 16.5% for adalimumab 160/80/40 versus 9.3% in the placebo group, p=0.019.

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Figure 2. Probability of remission at week 8 increases with increasing week 8 adalimumab trough concentrations. Logistic regression model of the probability of remission per Mayo score at week 8 as a function of week 8 adalimumab trough concentrations.



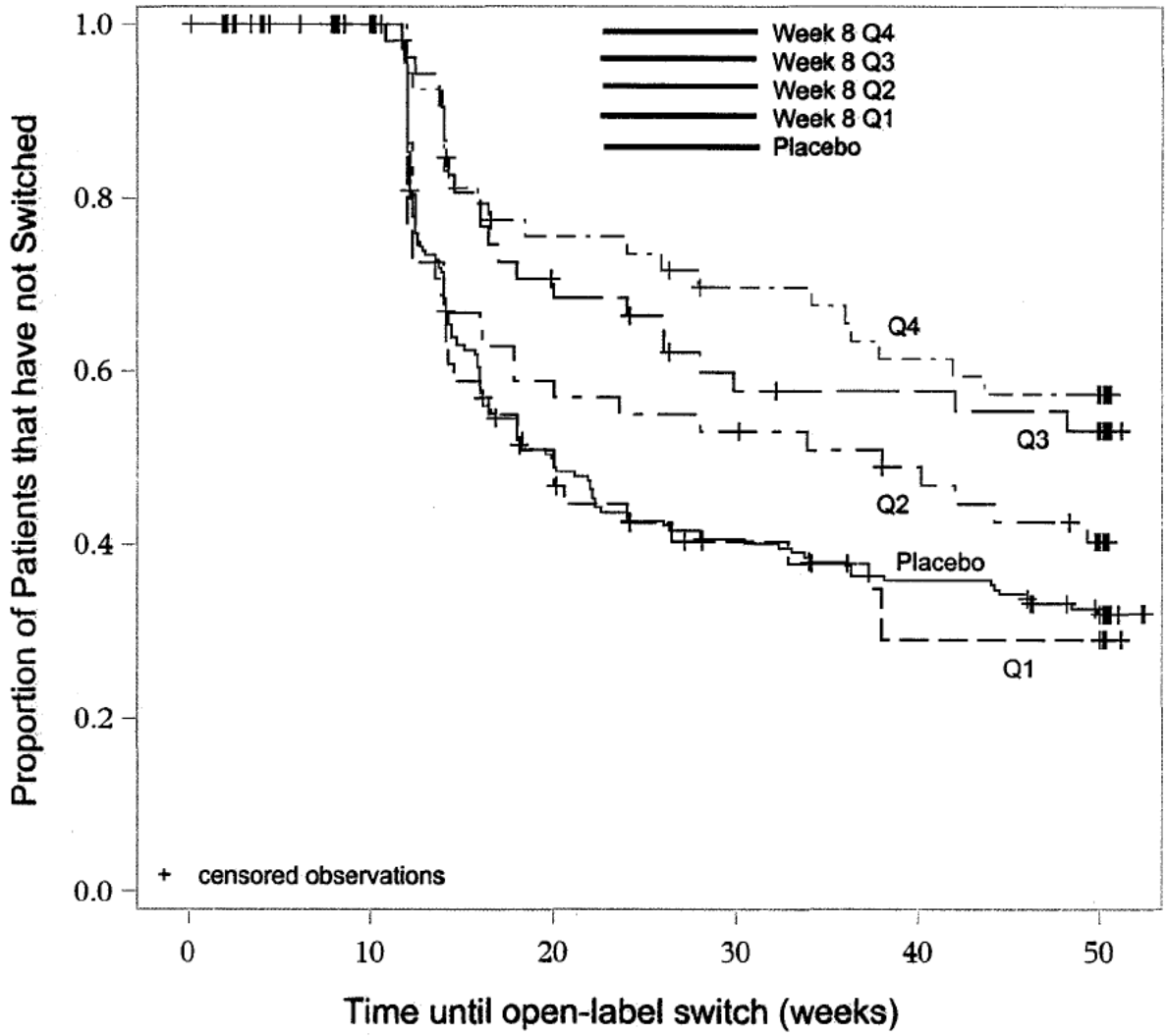
Logistic regression modeling was also performed using numerous risk factors. Baseline Mayo score ($p<0.0001$) and prior exposure to anti-TNF therapy ($p=0.022$) were the only risk factors which demonstrated a statistically significant relationship to week 8 remission. Multivariate logistic regression was performed to determine if the relationship between week 8 adalimumab trough concentration and week 8 remission was confounded. When adjusting for baseline Mayo score and prior exposure to anti-TNF therapy, the week 8 adalimumab trough concentration was still significant ($p=0.0003$).

Subjects who exhibited inadequate response during the maintenance phase were able to switch from their double-blind (DB) treatment assignment to open-label (OL) adalimumab 40 mg every other week (eow) starting at week 12. Kaplan Meier analysis was conducted to explore the relationship between week 8 concentrations and time to OL switch and to examine if an increase in concentration is associated with an increase time to open-label switch.

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Figure 3 demonstrates that subjects who had lower week 8 adalimumab trough concentrations exhibited inadequate response earlier than the subjects with higher week 8 concentrations. This provides additional evidence that exposures achieved by 160/80/40 induction dose may not be sufficient to maintain response. Proportional hazards analysis showed that week 8 concentrations are significantly associated with time to inadequate response after correcting for previous exposure to anti-TNF therapy and baseline mayo score.

Figure 3. Low Week 8 adalimumab concentration quartiles are associated with time to open label switch. Kaplan-Meier plot of the proportion of subjects who have not switched vs. week 8 adalimumab trough concentration quartile. Patients who did not switch to open label were censored and are indicated by the "+" symbol.



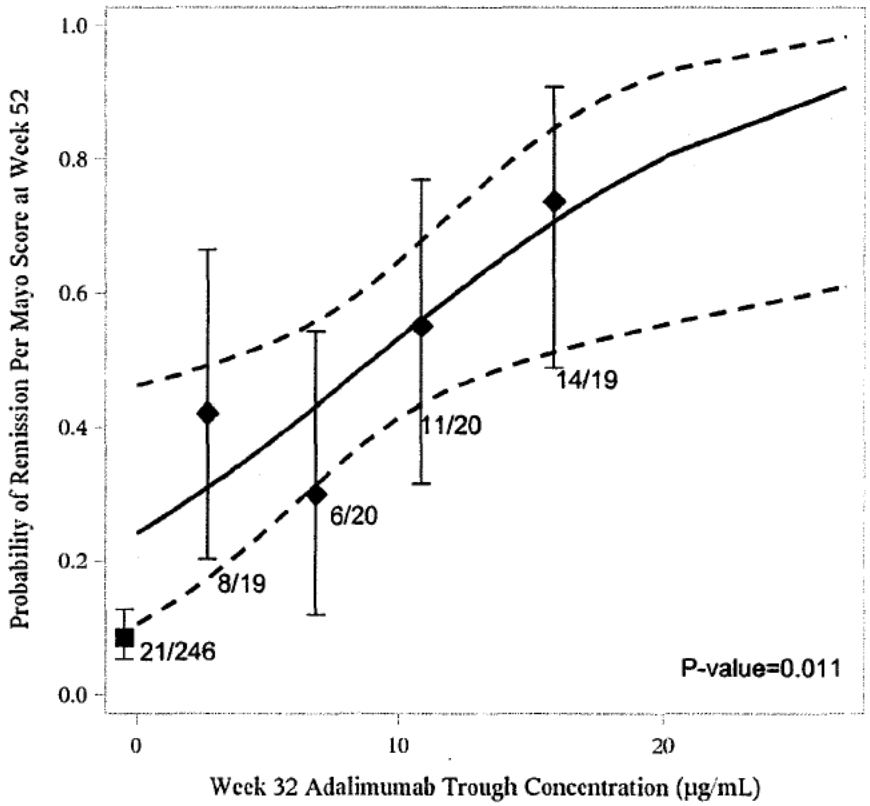
1.1.3 Does the exposure-response relationship for clinical remission at week 52 support the proposed dosing regimen for the maintenance phase?

A robust exposure-response relationship for the maintenance phase could not be established due to significant drop out and missing PK data. Two limitations of the exposure-response are (1) the analysis was based on only 78 patients (31% of the total treatment population) who remained in

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double-blind phase throughout the trial and had PK data and (2) the analysis dataset included non-responders (i.e., non-remitters) at week 8. Furthermore, only a marginally significant (p=0.04) exposure-response relationship was observed using a logistic regression analysis that adjusted for baseline mayo score and prior anti-TNF use. Moreover, the data used in this analysis may not be representative of the actual treatment population since the clinical remission rate based on mayo scores is 33% (43/132) for patients who remained in the double blind treatment phase compared to 50% (39/78) for subjects who remained in double blind phase and had PK data. While dose escalation was allowed in the trial, the study design does not permit evaluation of the effect of dose escalation on efficacy.

Figure 4. Probability of remission at week 52 increases with increasing week 32 adalimumab trough concentrations. Logistic regression model of the probability of remission per Mayo score at week 52 as a function of week 32 adalimumab trough concentrations.



1.2 Recommendations

Refer to section 1.1 of the clinical pharmacology review for the recommendations.

1.3 Label Statements

None.

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2 Pertinent regulatory background

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. As of November 2010, adalimumab has been approved for the treatment of inflammatory diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (Ps), and Crohn's disease (CD), the other primary form of IBD. The indication **under review is "Reducing signs and symptoms,** and inducing and maintaining induction of clinical remission in adult subjects with moderately to severely active ulcerative colitis who have had an inadequate response to **conventional therapy".**

The sponsor did not conduct phase 2 dose ranging studies and selected the dosing regimen approved **for the Crohn's Disease indication for the phase 3 adult** UC clinical trials. Three studies are relevant to this review; M06-826, M06-827, and M10-223. The M06-827 study is particularly important is it was the only study in which PK data was collected.

M06-826.

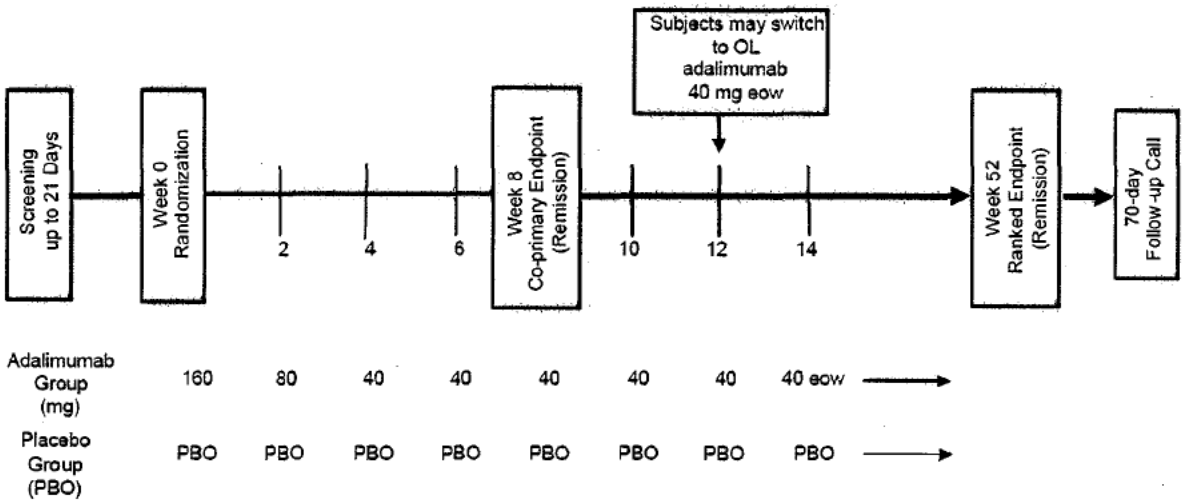
This study comprised of 8 to 12- week randomized, double-blind, placebo-controlled period followed by open-label treatment through Week 52. The primary objective was to assess the efficacy and safety of 2 dosing regimens (80/40/40 and 160/80/40) of adalimumab for the induction of clinical remission in subjects with moderately to severely active UC, and to assess maintenance of clinical remission during the open label period of the study. This study enrolled 576 subjects. The primary endpoint was clinical remission per Mayo score which is defined as total Mayo score ≤ 2 and no individual subscore > 1. Week 8 remission was 9.2% in the placebo arm and 18.5% in the adalimumab 160/80/40 arm (P=0.031). The low dosing regimen (80/40/40) had a 10.0% clinical remission rate at week 8 which was not significantly different from placebo (P=0.833).

M06-827

Sponsor conducted study M06-827 which was a phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of the human anti- Tumor necrosis factor (TNF) monoclonal antibody adalimumab in subjects with moderately to severely active ulcerative colitis. The secondary objective of this study was to assess the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration.

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Figure 5. Study M06-827 study design.



(Source : m06827-body – CSR.pdf)

There were 518 subjects who enrolled in Study M06-827. The ranked co-primary efficacy endpoints were the proportion of subjects who achieved remission at Week 8 and the proportion of subjects who achieved remission at Week 52. Week 8 remission was achieved by 9.3% of subjects in the placebo arm and 16.5% of subjects in the adalimumab 160/80/40 arm (P=0.019). Week 52 remission was achieved by 8.5% of subjects in the placebo arm and 17.3% of subjects in the adalimumab 160/80/40 arm (P=0.004).

M10-223

The objective of this study is to evaluate the long-term maintenance of response, safety, and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827.

Safety

Sponsor determined there were few significant differences between placebo and adalimumab treatment in terms of frequency, severity, and relationship **to study drug for common AE's, SAE's, and discontinuations due to AE's. The safety profile** observed throughout the study was consistent with previous clinical studies for adalimumab, and no new safety signals were observed. The most frequently reported treatment emergent adverse event in all analysis sets was colitis ulcerative (12.2% in the placebo group and 7.4% in the total adalimumab group during induction, 16.6% in the placebo group and 16.7% in the adalimumab 160/80/40 group during maintenance).

3 Results of Sponsor's Analysis

Population pharmacokinetic analyses were performed to estimate adalimumab apparent clearance and apparent volume of distribution of central compartment in subjects with UC. Further, pharmacokinetic parameters to be estimated are the absorption rate constant, the inter-compartmental clearance and the volume of the peripheral compartment.

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The structure of the starting pharmacokinetic model was based on observations from a population pharmacokinetic analysis performed with data collected from studies with adult rheumatoid arthritis subjects. In these previous studies a one compartmental model with first-order absorption from the depot compartment and first order elimination from the central compartment was appropriate for describing adalimumab pharmacokinetics when only trough concentrations are available. However, changeover to a two-compartment model led to a significant improvement of the objective function.

Population PK analyses were performed in NONMEM to estimate the apparent clearance and apparent volume of distribution of central compartment and volume of distribution of the peripheral compartment of adalimumab in subjects with UC. Body weight, occurrence of AAA, and plasma concentration of albumin were determined as significant covariates on the apparent clearance.

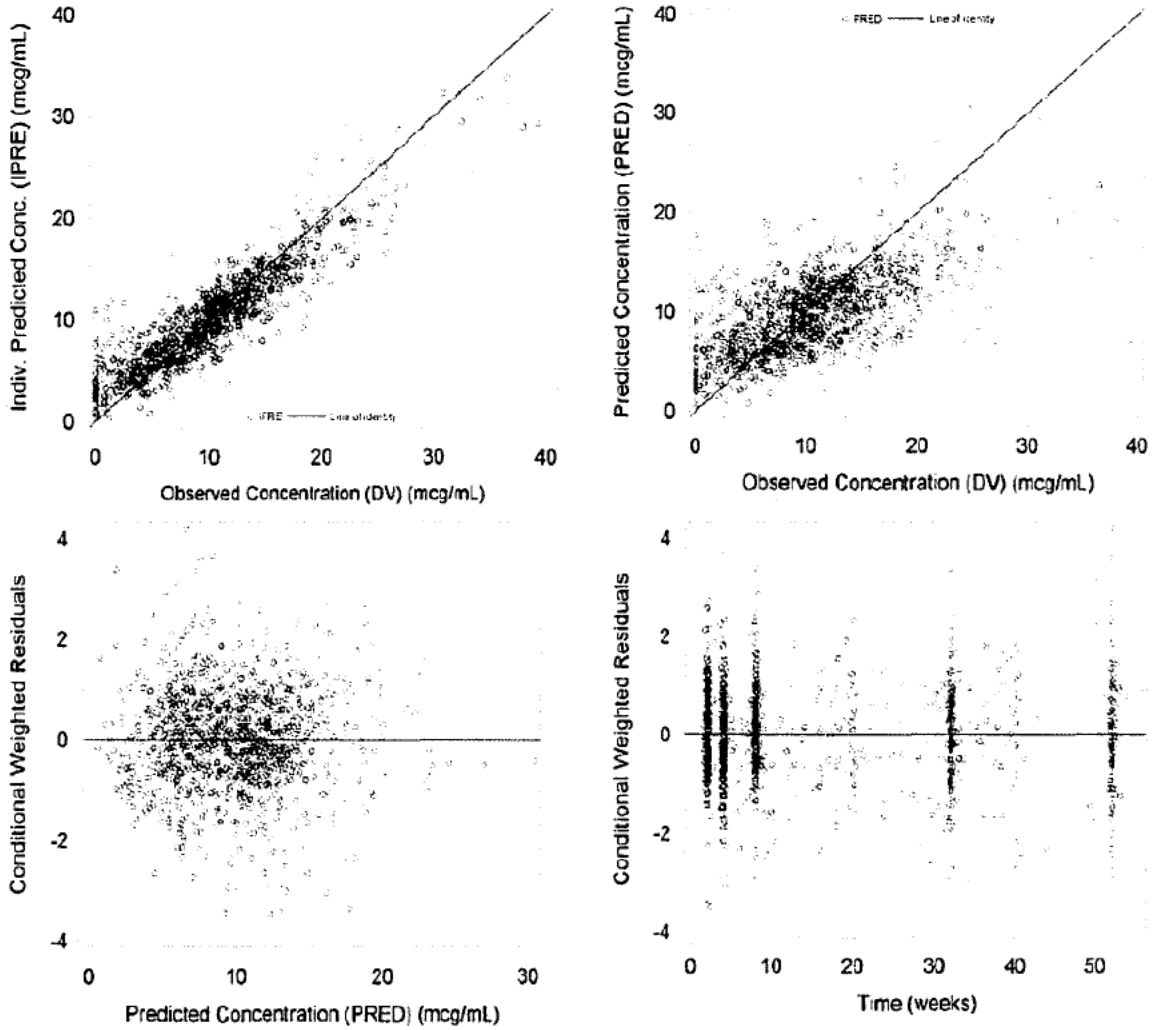
Population PK Parameter Estimates

The CL/F of adalimumab was 0.37 L/d (15.2 mL/h), V2/F was 4.80 L, and V3 was 4.18 L. An increase of body weight by 10 kg is expected to increase CL/F by approximately 13%. The presence of AAA leads to approximately double the CL/F. A similar impact of body weight and AAA on adalimumab PK parameters has been observed in subjects with RA, JIA, AS, PsA, and CD. Plasma albumin was tested as a covariate for the first time for adalimumab based on published results from a population PK model for infliximab in subjects with UC. An increase in plasma albumin concentration by 1 g/dL is expected to decrease CL/F of adalimumab by approximately 41%, and the effect is comparable to that reported for infliximab.

Sponsor concluded that no dosage adjustment of adalimumab based on covariates is warranted.

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Figure 6. Goodness of fit plots. Individual (upper left) and population (upper right) predicted versus observed concentrations and conditional weighted residuals versus predicted concentrations (lower left) and versus time (lower right) for final population pharmacokinetic model.



(source: m06827-pk-legacy.pdf, Figure 9, Page 108).

Reviewer's Comments.
Overall, the population pharmacokinetic analysis conducted by the sponsor is acceptable.

- *Simulations suggest that splitting the 160 mg initial dose to 80 mg on day 1 and 80 mg on day 2 produces minimal impact on the concentration profile of adalimumab. This observation is supported by fact that the drug has a half life of ~2 weeks which is significantly longer than the interval between the consecutive 80 mg doses.*
- *Based on understanding of the physiology, subjects who have AAA positive states are likely to clear drug faster and sponsor concluded that the clearance in these individuals was approximately double compared to AAA negative subjects. However, due to limitations of the assay, samples which contained ≥ 2 microgram/mL adalimumab were not tested for AAA status*

but were classified AAA negative. Thus, true magnitude of effect of AAA status on clearance cannot be estimated. Please refer to section 2.6 of the clinical pharmacology QBR for more details.

- *Sponsor did not conduct exposure-response analysis for efficacy or safety. Reviewer conducted exposure-response for efficacy for the primary endpoints to examine if the proposed dosing regimen is appropriate.*

4 Reviewer's Analysis

4.1 Introduction

This review will address the impact of splitting the induction dose. Next, the exposure-response relationship will be characterized for the primary endpoints. Finally, this review will assess the proposed dose regimen in context of the exposure-response relationship for efficacy.

4.2 Objectives

- Determine if the PK analysis supports splitting the initial 160 mg dose as 80 mg on the first day and 80 mg on the second day
- Investigate if there is evidence of an exposure-response relationship for efficacy.
- Determine if the exposure-response relationships support the proposed dosing regimen for the induction and the maintenance phase.

4.3 Methods

The effect of splitting the initial 160 mg dose as 80 mg on the first day and 80 mg on the second day was determined by simulating the two dosage regimens **using the sponsor's final population PK model.**

The potential relationship between the two primary endpoints and the corresponding trough adalimumab concentrations was assessed. The ranked co-primary efficacy endpoints are the clinical remission per Mayo score at week 8 (induction endpoint) and clinical remission per Mayo score at week 52 (maintenance endpoint).

Clinical remission per Mayo score is defined as a Mayo score ≤ 2 and no individual subscore > 1. The Mayo score is a composite score of UC disease activity ranging from 0 to 12 based on the sum of 4 subscores: endoscopy (0-3), stool frequency (0-3), **rectal bleeding (0-3), and physician's global** assessment (0-3).

4.3.1 Data Sets

Data sets used are summarized in Table 1.

Table 1. Analysis Data Sets

Study Number	Name	Link to cdsnas
M06-827	treat.xpt	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\Sponsor Data and Reports
M06-827	pk-dataset.xpt	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\Sponsor Data and Reports

Reference ID: 3200370

M06-827	mayo.xpt	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\Sponsor Data and Reports

4.3.2 Software

The following software packages were used in the analyses.

- SAS version 9.2
- NONMEM version 6
- R version 2.10.1
- MS Excel 2003

4.3.3 Models

Pharmacokinetic simulations of the alternative split-dose induction regimen were performed using the **sponsor's final population PK model (see sponsor's a**nalysis section). The post hoc estimates for 353 subjects from the population PK model were used to simulated adalimumab concentration time profile over a period of 4 weeks.

The relationship between probability of achieving clinical remission at week 8 and adalimumab week 8 trough concentrations was modeled using logistic regression. The relationship between achieving clinical remission at week 52 and adalimumab week 32 trough concentrations was also modeled using logistic regression. Data from only 78 patients who remained in double blind phase in the treatment arm and had PK were included in the analysis. Week 32 is the last time the adalimumab concentration was measured before the assessment of week 52 remi**ssion and since the drug's ha**lf-life is ~14 days, it is reasonable to assume that steady-state was achieved by week 32. An exposure-response relationship would be apparent if an increase in adalimumab week 8 trough concentrations was accompanied by an increase in the probability of achieving clinical remission at week 8 or if an increase in adalimumab week 32 trough concentration was accompanied by an increase in the probability of achieving clinical remission at week 52.

Numerous patient risk factors (such as age, baseline Mayo score, previous exposure to anti-TNF therapy, weight, etc.) were each tested in a univariate logistic regression model with week 8 remission. Statistically significant risk factors were incorporated in a multivariate logistic regression model to determine week 8 adalimumab trough concentrations were still significant after correction for these factors.

A Kaplan-Meier plot displayed the proportion of subjects who did not switch to open-label versus time for the four adalimumab week 8 trough concentration quartiles and placebo. A subject was switched to open-label if they demonstrated an inadequate response to therapy. Inadequate response was defined as:

- Partial Mayo score $\geq$ baseline score on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 4 to 7 at Baseline)
- Partial Mayo score $\geq$ 7 on 2 consecutive visits at least 14 days apart (for subjects with a partial Mayo score of 8 or 9 at Baseline)

The time to open label switch was expressed in weeks after the initial dose. Subjects were censored if they dropped out or did not switch to open label until end of the study.

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A univariate proportional hazards model was applied to model the relationship between time to inadequate response and week 8 adalimumab trough concentrations as well as numerous subject risk factors (such as as age, baseline Mayo score, previous exposure to anti-TNF therapy, weight, etc.). Statistically significant risk factors were included in a multivariate proportional hazards model to determine if week 8 adalimumab trough concentrations were still significant after correction for these factors.

4.3.4 Results

Simulated split dosing

Splitting the initial 160 mg dose as 80 mg on the first day and 80 mg on the second day did not produce a significant change in the simulated concentration profile (see Figure 1). Within one week, the simulated concentration profile for the 160 mg dose was nearly indistinguishable from the concentration profile obtained when administering 80 mg on the first day and 80 mg on the second day. This conclusion is further supported by the long terminal half-life of adalimumab (~2 weeks).

Exposure-Response Remission at Week 8

Logistic regression modeling resulted in a statistically-significant relationship ($p=0.0002$) between remission at week 8 and week 8 adalimumab trough concentration (see figure 2). Univariate logistic regression was performed using risk factors (such as age, baseline Mayo score, prior exposure to anti-TNF therapy, weight, etc.) to determine if the factors might be associated with remission status. Significant relationships were discovered between week 8 remission and baseline mayo score ($p<0.0001$) and prior anti-TNF therapy ($p=0.0219$). When a subject has had prior exposure to anti-TNF therapy, the model predicts that the subject is less likely to achieve week 8 remission than a subject without prior exposure. The model also predicts that as baseline mayo score decreases, the probability of week 8 remission increased. One potential explanation for this observation could be that the less severe subjects with lower mayo scores **are "closer" to remission and may require less** therapeutic intervention to achieve remission than the subjects with higher mayo scores.

In order to examine if concentrations are the is the driver for week 8 remission, multivariate logistic regression was performed using the each variable that produced a statistically significant relationship with week 8 remission in the univariate logistic regression model. The multivariate logistic regression showed that week 8 adalimumab trough concentration ($p=0.0003$), baseline mayo ($p<0.0001$), and prior-anti-TNF therapy ($p=0.0253$) all produced statistically significant relationships to week 8 remission. The ER relationship for week 8 remission suggests that a higher dose may lead to improved remission rate.

A Kaplan-Meier plot was generated to track the proportion of subjects that have undergone an open-label switch (inadequate therapeutic responders) versus time since first dose. The subjects were grouped into -week 8 adalimumab trough concentration quartiles and a placebo group (see figure 3). The plot suggests that subjects with higher week 8 concentrations maintain response over a longer period of time compared to subjects with lower week 8 concentrations who switch to open label earlier. In addition, the proportion of subjects that did not switch open label increases with increasing concentration (32% for placebo, 29% for Q1, 40% for Q2, 53% for Q3, and 57% for Q4).

A univariate proportional hazards model was generated using week 8 adalimumab trough concentration as well as various subject risk factors (such as age, baseline Mayo score, prior exposure to anti-TNF therapy, weight, etc.) as covariates. The week 8 adalimumab concentration ($p=0.0006$) and prior exposure to anti-TNF therapy ($p=0.0031$) produced statistically significant relationships to the

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time to open-label switch. A multivariate proportional hazards model shows that week 8 adalimumab concentration is still significant (p=0.0008) after correcting for prior exposure to anti-TNF therapy, which is also significant (p=0.0042). The hazard ratio for week 8 adalimumab trough concentration (HR=0.928) indicates that increasing the concentration by 1 μg/mL decreases hazard for open-label switch by 7.2%. The hazard ratio for prior exposure to anti-TNF therapy (HR=0.573) means that no prior exposure is associated with 42.7% lower hazard for open-label switch compared to having prior exposure.

The baseline Mayo score was not significant (p=0.39) in spite of the relationship to week 8 remission established with the logistic regression model. Despite the non-significant value, the baseline Mayo score was included in a multivariate proportional hazards model with prior exposure to anti-TNF therapy and week 8 adalimumab trough concentration. The multivariate proportional hazards model showed that baseline Mayo score was still not significant (p=0.75) whereas prior exposure to anti-TNF therapy (p=0.005) and week 8 adalimumab trough concentration (p=0.001) were significant. The results suggest that increased time to open-label switch increases with increasing concentration even when correcting for potentially confounding risk factors.

This submission did not present any new safety signals. In addition to the lack of new safety signals, exposure-safety analysis performed by the FDA review **of the Crohn's disease indication demonstrated** that exposure is unrelated to serious adverse events, serious infections, urinary infections, and herpes **simplex in Crohn's Disease subjects (see BLA** 125057 clinical pharmacology review by Drs. Tien Mien Chen and Christoffer W. Tornoe for more details).

Exposure-Response for Remission at Week 52

A logistic regression model (p=0.0113) was established relating week 32 adalimumab trough concentration and clinical remission at week 52 (maintenance phase) (see figure 4). Though the trend suggests that an increase in week 32 adalimumab trough concentration is associated with increased week 52 remission, there are numerous limitations to this analysis highlighted in section 1.1.3.

Acknowledging these limitations, the possibility of using higher maintenance dose cannot be supported from an exposure-response perspective. While dose escalation was allowed in the trial, the study design does not permit evaluation of the effect of dose escalation on efficacy. It is important to note that sponsor evaluated the efficacy for 40 mg ew adalimumab for maintaining clinical remission in **Crohn's disease clinical trials (see** approved label for Humira). It was demonstrated that 40 mg ew did not provide additional benefit over 40 mg eow dosing regimen.

Reference ID: 3200370

5 Listing of Analyses Codes and Output Files

Table 2. Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
convert_xpt_to_csv_create_sim_data v1_2.sas	Converts the xpt pk dataset to a csv file which can be used as the input for NONMEM simulation.	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 1
pk_sim_ind_final_csv.csv	This file is the a csv representation of the sponsor pk data, used for NONMEM simulation	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 1
run3SIM_IND.mod	NONMEM simulation script	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 1
ıb3SIM_IND.csvX	Contains simulated PK profiles generated from NONMEM	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 1
open_and_plot_ind_simulation_results_v1_2.sas	Opens and plots the simulation data	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 2
Plot - series - percentile - 160 given over 1 and 2 days - 80 day 14.png	Figure 1. Adalimumab PK profiles comparing the two induction dosing regimens: 160 mg administered on day 1 or 80 mg administered on Day 1 and 2. Both regimens receive an additional 80	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group1

Reference ID: 3200370

	mg dose on day 14.	
exposure_response_v2_19.sas	Exposure response analysis	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Model Name 3
Probability of Remission Per Mayo Score at Week 8 - vs DV at week 8 - with mean and 95 percent CI in quantiles - TX and placebo used in analysis.png	Plot of logistic regression model of the probability (mean and 95% CI) of remission per Mayo score at week 8 versus adalimumab trough concentration at week 8.	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Plot - time-to-open-label-switch - in each week 8 conc quartile.png	Kaplan-Meier plot of the proportion of subjects who have not switched vs. week 8 adalimumab trough concentration quartile.	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Plot - Probability of Remission Per Mayo Score at Week 52 - vs DV at Week 32 - with mean and 95 percent CI in quantiles - TX only used in analysis.png	Logistic regression model of the probability of remission per Mayo score at week 52 as a function of week 32 adalimumab trough concentrations.	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Table - p-values for logistic regression - univariate - Remission - Week 8 - TX and PBO.pdf	Table of p-values from univariate LR	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Table - p-values for logistic regression - multivariate - Remission - Week 8 - TX and PBO.pdf	Table of p-values from multivariate LR	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Table - p-values for proportional hazards	Table of p-	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing

ression - univariate - Remission - Week 8 - only.pdf	values from univariate PH	PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
able - p-values for proportional hazards regression - multivariate 3 inputs - Remission - Week 8 - TX only.pdf	Table of p-values from multivariate PH	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Table - p-values for proportional hazards regression - multivariate 2 inputs - Remission - Week 8 - TX only.pdf	Table of p-values from multivariate PH	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2
Table - Kaplan-Meier Plot Final Survival Proportions - Remission - Week 8 - TX and PBO.pdf	The proportion of subjects that did not switch open label versus concentration	\\cdsnas\PHARMACOMETRICS\Reviews\Ongoing PM Reviews\Adalimumab_BLA125057_MB\ER Analyses\Graphs Group2

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Review Summary

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-dose, 1 mL prefilled glass syringe.

In December 2002, adalimumab was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) in the United States (US). On 27 February 2007, adalimumab was approved in the US for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Adalimumab has also been approved for indications in psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis.

The purpose of this submission is to submit an efficacy supplement for a new indication in adalimumab for reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The submission is based upon data from the following studies:

- Study M06-826, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

- Study M06-827, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction and Maintenance of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis"

- Interim results from Study M10-223, entitled "A Multicenter, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Long Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects With Ulcerative Colitis"

Reference ID: 3200370

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

The pharmacokinetics (PK) of adalimumab was evaluated in subjects with moderately to severely active ulcerative colitis (UC) in PK Study M06-827. The population pharmacokinetics of adalimumab was also evaluated for UC subjects using a non-linear mixed effects modeling (NONMEM) approach using data from PK Study M06-827. The impact of covariates on adalimumab pharmacokinetics was assessed.

The results (PK Study M06-827) were compared with results from previous studies in subjects with Crohn's disease (CD) in which subjects were administered a 4-week 160 mg/80 mg induction regimen (PK Study M02-403) and a 52-week 40 mg maintenance regimen (PK Study M02-433). The pharmacokinetics of adalimumab following a 4-week induction regimen were also evaluated in subjects with moderate to severe Crohn's disease who had lost response or were intolerant to infliximab in PK Study M04-691.

The immunogenicity of adalimumab was examined in all aforementioned studies (PK Study M06-827, PK Study M02-403, PK Study M02-433 and PK Study M04-691). The impact of immunogenicity on efficacy and safety were assessed.

Overall, the sBLA is filable from the clinical pharmacology standpoint. The clinical pharmacology review will review the comparison of adalimumab PK and immunogenicity results between UC and CD studies. A pharmacometric review which will focus on the popPK analysis and trial simulation for dosing regimen support in the labeling.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125-057	Brand Name	Humira
OCP Division (I, II, III, IV, V)	DCP III	Generic Name	Adalimumab
Medical Division	DGIP	Drug Class	Recombinant human IgG1
OCP Reviewer	Lanyan Fang, Ph.D.	Indication(s)	Ulcerative Colitis
OCP Secondary Reviewer	Gilbert Burckart, PharmD	Dosage Form	PFS or pen
Pharmacometrics Reviewer Secondary Reviewer	Lanyan Fang, Ph.D. Christine Garnett, Pharm.D.	Dosing Regimen	160 mg Day 1, 80 mg Day 15, followed by 40 mg every other week starting Day 29
Date of Submission	Jan 25, 2011	Route of Administration	S.C.
Estimated Due Date of OCP Review	8/25/2011	Sponsor	Abbott
Medical Division Due Date	9/25/2011	Priority Classification	Standard
PDUFA Due Date	11/25/2011	Dosing Strength	40 mg/vial

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		
Reference Bioanalytical and Analytical Methods	X	4		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

gender:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**4**		**Pop PK and Trail simulation were used in the submission to support dosing regimen in the labeling**
Immunogenicity	**X**	**2**		**Assess impact of immunogenicity on efficacy and safety**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**15**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Covariate analysis in the popPK analysis
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

Fileable.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Lanyan Fang, Ph.D. — 3-9-11

Clinical Pharmacology Reviewer — Date

Gilbert Burckart, Pharm.D. — 3/10/11

Acting Team Leader — Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	September 14, 2012
Reviewer(s):	Teresa McMillan, PharmD Division of Medication Error Prevention &Analysis
Team Leader:	Lubna Merchant, PharmD Division of Medication Error Prevention &Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention &Analysis
Drug Name(s) and Strength(s):	Humira (Adalimumab) Injection 40 mg/0.8 mL Prefilled Pen, 20 mg/0.4 mL Prefilled Syringe, 40 mg/0.8 mL Prefilled Syringe
Application Type/Number:	BLA/125057
Submission Number:	232
Applicant/sponsor:	Abbott Laboratories, Inc
OSE RCM #:	2012-1576

*** This document contains proprietary and confidential information that should not be released to the public.***

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1.2 Regulatory History 3
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2 Methods and Matertials Reviewed 3
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3 Discussion 4
4 Conclusions and Recommendations 4
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Reference ID: 3189280

1 INTRODUCTION

This review evaluates the proposed insert and carton labeling and the Medication Guide for Humira (adalimumab) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

On January 25, 2011, the Applicant submitted a supplemental Biologics License Application for the addition of a new indication for Humira (adalimumab) for reducing the signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. This supplement received a Complete Response on November 21, 2011. On March 30, 2012, the Applicant resubmitted this supplemental BLA Application.

1.2 REGULATORY HISTORY

Humira was approved in December 2002 to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. In 2008, two additional indications, juvenile idiopathic arthritis and plaque psoriasis, were approved.

1.3 PRODUCT INFORMATION

The following product information is provided in the March 30, 2012 submission.

- Active Ingredient: Adalimumab
- Indication of Use: Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis, Ulcerative Colitis
- Route of Administration: Subcutaneous
- Dosage Form: Solution
- Strength: 20 mg/0.4 mL, 40 mg/0.8 mL, 40 mg/0.8 mL
- Dose and Frequency: 20 mg, 40 mg, 80 mg, or 160 mg every other week
- How Supplied: Pre-filled syringe and Single-use Pen
- Storage: Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F) and should be protected from exposure to light.

2 METHODS AND MATERIALS REVIEWED

2.1 SELECTION OF MEDICATION ERROR CASES

An AERS search was not conducted for this supplement because we have been actively monitoring medication errors with this product. There have been reports of incomplete injection and accidental firing associated with the Humira Pen. The issues have been discussed in OSE Reviews #2012-578, #2001-2102 and #2009-935. This supplement involves the addition of a new indication and does not directly involve the issues discussed above.

Reference ID: 3189280

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling and the Medication Guide submitted on March 30, 2012 (no image available)
- Carton Labeling submitted on March 15, 2011 (See Appendix B for image)

3 DISCUSSION

The Applicant is proposing a new indication, Ulcerative Colitis to be added to the insert labeling and the Medication Guide. The dosage and administration for the proposed Ulcerative Colitis indication is the same as the currently approved Crohn's Disease indication with the exception that Humira should only be continued in patients who have responded to Humira during the first 8 weeks of therapy. For patients who respond and then lose their response, consideration may be given to increasing the dosing frequency of Humira to 40 mg every week from the maintenance dosing frequency of 40 mg every other week.

Additionally, the insert labeling states that the starting dose for the proposed Ulcerative Colitis indication will be supplied the same as the Crohn's Disease Starter Package. The carton labeling is also the same as the currently approved Crohn's Disease Starter Package with the addition of a change to the heading to "Crohn's Disease/Ulcerative Colitis Starter Package". This is acceptable because the initiation doses for both indications are the same.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed insert and carton labeling and the Medication Guide are acceptable and we have no recommendations to be implemented prior to approval of this BLA supplement.

If you have further questions or need clarifications, please contact Nitin Patel, project manager, at 301-796-5412.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B-Proposed Carton Labeling

2 Pages of Draft Labeling have been Withheld in Full as b4 (TS/ CCI) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
09/14/2012

LUBNA A MERCHANT
09/14/2012

SCOTT M DALLAS
09/14/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 13, 2012
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	HUMIRA (adalimumab)
Dosage Form and Route:	Injection, Solution for Subcutaneous use
Application Type/Number:	BLA 125057/232
Applicant:	Abbott Laboratories

1 INTRODUCTION

On March 30, 2012, Abbott Laboratories submitted for the Agency's review a Complete Response in response to an FDA Complete Response Letter, dated November 21, 2011, for a supplement to their Biologics License Application (BLA) 125057/232 for HUMIRA (adalimumab) injection. This supplement proposes a new indication for HUMIRA (adalimumabe) injection for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosupressants, such as corticosteroids, azathiprine or 6- mercaptopurine (6-MP). No revisions to the currently approved Instructions for Use (IFU) (dated May 24, 2012) were proposed. HUMIRA was originally approved on December 31, 2002. On July 12, 2012, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and IFUs for HUMIRA (adalimumab).

This review is written in response to a request by DGIEP for DMPP to review the Applicant's proposed Medication Guide (MG) for HUMIRA (adalimumab) injection.

2 MATERIAL REVIEWED

- Draft HUMIRA (adalimumab) injection Medication Guide (MG) received on March 30, 2012, revised by the Review Division and received by DMPP on September 12, 2012.
- Draft HUMIRA (adalimumab) injection Single-Use Pen and Single-Use Prefilled Syringe Instructions for Use received on March 30, 2012, revised by the Review Division and received by DMPP on September 12, 2012.
- Draft HUMIRA (adalimumab) Prescribing Information (PI) received on March 30, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 6, 2012 and September 12, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG and Instructions for Use we have:

- performed a focused review of the proposed revisions to the Prescribing Information (PI) and MG
- performed a focused review of the Instructions for Use, revising the current sharps disposal language to reflect current patient labeling practice regarding standard sharps disposal language to be included in CDER IFUs
- simplified wording and clarified concepts where possible
- ensured that the MG and Instructions for Use are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and Instructions for Use are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and Instructions for Use is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and Instructions for Use.

Please let us know if you have any questions.

76 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

SHARON R MILLS
09/13/2012

LASHAWN M GRIFFITHS
09/13/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion
Division of Consumer Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 10, 2012

To: Kevin Bugin, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Kendra Y. Jones, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: BLA 125057/232
OPDP labeling comments for HUMIRA (adalimumab) injection, for subcutaneous use

---

OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for HUMIRA (adalimumab) injection, for subcutaneous use (Humira) submitted for consult on July 12, 2012, and offers the following comments.

OPDP's comments on the PI and Medication Guide are based on Version 16 of the proposed draft marked-up labeling titled, "uspi-0060.doc" accessed via the eRoom.

OPDP's comments on the PI and Medication Guide are provided directly in the marked-up document below.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding the PI, please contact Katie Klemm at 301-796-3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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77Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Reference ID: 3186829

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/s/

KENDRA Y JONES
09/10/2012

Selected Requirements of Prescribing Information

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**HUMIRA (adalimumab) injection, for subcutaneous use**
Applicant	Abbott
Application/Supplement Number	BLA 125057/S-232
Type of Application	Efficacy supplement
Indication(s)	Ulcerative colitis is the proposed indication in this efficacy supplement. Humira is approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis.
Established Pharmacologic Class[1]	Tumor necrosis factor (TNF) blocker
Office/Division	ODEIII/DGIEP
Division Project Manager	Kevin Bugin
Date FDA Received Application	March 30, 2012
Goal Date	September 28, 2012
Date PI Received by SEALD	September 10, 2012
SEALD Review Date	September 11, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *Abbott was granted a waiver of the 1/2 requirement for the length of the HL for a prior sBLA.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *Include the supplement approval date.*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

NO 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *The vertical lines do not correspond to the new or modified text in the FPI.*

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it

is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ERIC R BRODSKY
09/11/2012

LAURIE B BURKE
09/12/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 9/14/2011

TO: Kevin Bugin
Regulatory Project Manager
Division of Gastroenterology

FROM: Khairy W. Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Jean Mulinde, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125057/STN-232

APPLICANT: Abbott Laboratories

DRUG: Humira (adalimumab)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: To add ulcerative colitis to the current indication

CONSULTATION REQUEST DATE: 3/22/2011

Reference ID: 3200370

Inspection Summary Goal Date: 9/15/2011

PDUFA DATE: 11/25/2011

Protocol: Protocol: M06-826 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Human Anti-TNF Monoclonal Antibody Adalimumab for the Induction of Clinical Remission in Subjects with Moderately to Severely Active Ulcerative Colitis".

I. BACKGROUND:

Adalimumab, is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. Adalimumab was first approved in the US in 2002 for treatment of rheumatoid arthritis, and then for Crohn's disease (CD).

The objective of this study is to assess the efficacy and safety of adalimumab for the induction of clinical remission in subjects with moderately to severely active UC.

II. RESULTS (by Site): There was only one site inspected:

Name of CI/Address	Protocol # and # of Subjects	Inspection Date	Final Classification
Susan Greenbloom, M.D. Toronto Digestive Disease Assoc. 4600 Highway 7, Unit #225 Vaughn, ON L4L 4Y7, Canada	M06-826 Site # 29080 53 Subjects	July 14-20, 2011	Pending (Preliminary Classification NAI)

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has been received from the field, but a complete review of EIR is pending.

Name of Clinical Investigator: Susan Greenbloom, M.D.

a. **What was inspected:** The field investigator reviewed the records of 22 subjects and compared source documents with CRFs and the NDA data listings. Documents reviewed included informed consent forms, inclusion/exclusion criteria, IRB approvals, protocol deviations, adverse events reporting and drug accountability records.

b. General observations/commentary: No regulatory violations were observed during the inspection and a Form FDA 483 was not issued.

Note: Observations noted for this site are based on informal communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon final review of the Establishment Inspection Report.

c. Assessment of data integrity: The data obtained from this clinical site are reliable based on available information and can be used in support of the respective indication for BLA 125057 STN-232.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data obtained from Site 29080, that of Dr. Greenbloom, are reliable based on available information and can be used in support of the respective indication for BLA 125057 STN-232.

Note: All observations noted above are based on the preliminary communications provided by the FDA field investigator and preliminary review of inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon complete review of the EIR.

Follow-Up Actions: OSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIR and supporting inspection evidence and exhibits.

/Khairy W. Malek, M.D., Ph.D./
Khairy W. Malek, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

/Lauren Iacono-Connors, Ph.D./
Lauren Iacono-Connors, Ph.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

Jean Mulinde, M.D.

/Jean Mulinde, M.D./
Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: BLA125057/232 Prior Approval Efficacy Supplement

Name of Drug: Humira (adalimumab) solution for subcutaneous injection, 40 mg/0.8 mL and 20 mg/0.4 mL

Applicant: Abbott Laboratories

Labeling Reviewed

Submission/Recipt Date: January 25, 2011 and March 25, 2011.

Background and Summary Description

In December 2002, adalimumab was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) in the United States (US). On 27 February 2007, adalimumab was approved in the US for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Adalimumab has also been approved for indications in psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis.

The current prior approval supplement provides for the new indication of reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The March 25, 2011 amendment includes revised labeling based on a DPARP labeling supplement approval to include additional safety information in the label.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X." For this review the January 25, 2011 SPL converted to PDF was reviewed.

Reference ID: 3200370

Recommendations

All labeling issues identified on the following pages with an "X" will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by April 29, 2011 The resubmitted labeling will be used for further labeling discussions.

Highlights (HL)

- **General comments**

☒ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

☐ A horizontal line must separate the HL and Table of Contents (TOC).

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and bold type.

☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)

Reference ID: 3200370

• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, bolded, and read as follows: "These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)."
- **Product Title**
  - ☐ Must be bolded and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
  - ☐ All text in the boxed warning is bolded.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, bolded letters containing the word "WARNING" and other words to identify the subject of the warning (e.g.,"WARNING: LIFE-THREATENING ADVERSE REACTIONS").
  - ☐ Must have the verbatim statement "See full prescribing information for complete boxed warning." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☒ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

Reference ID: 3200370

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

☐ All contraindications listed in the FPI must also be listed in HL.

☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

☐ For drug products other than vaccines, the verbatim bolded statement, "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

☐ Must include the verbatim statement: "See 17 for Patient Counseling Information" or if the product has FDA-approved patient labeling: "See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide").

- **Revision Date**

☒ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading FULL PRESCRIBING INFORMATION: CONTENTS must appear at the

Reference ID: 3200370

beginning in UPPER CASE and bold type.

- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in bold type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – FULL PRESCRIBING INFORMATION – must appear at the beginning in UPPER CASE and bold type.
  - ☒ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, bold type, containing the word "WARNING" and other words to identify the subject of the warning. Use bold type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling.

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Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

☒ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

☐ This section is required and cannot be omitted.

☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Regulatory Project Manager — Date 4/8/11

Chief, Project Management Staff — Date 4/8/11

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RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # BLA# 125057	NDA Supplement #:S- BLA STN # 125057/232	Efficacy Supplement Type SE-1
Proprietary Name: Humira Established/Proper Name: adalimumab Dosage Form: Solution (subcuetaneous) Strengths: 40 mg/0.8 mL and 20 mg/0.4 mL		
Applicant: Abbott Laboratories Agent for Applicant (if applicable):		
Date of Application: 01/25/2011 Date of Receipt: 01/25/2011 Date clock started after UN:		
PDUFA Goal Date: 11/25/2011	Action Goal Date (if different):	
Filing Date: 03/26/2011	Date of Filing Meeting: 03/08/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products

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	☐ Other (drug/device/biological product)

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☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 100103	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

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User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes,** please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***		X		Canasa received Orphan designation for pediatric IBD

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If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes,** # years requested: ***Note:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*			X	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			X	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no, explain.**				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes,** BLA #			**X**	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

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Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff:*			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note:*** *NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			Supplement contains pediatric plan, waiver and deferral request.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		X		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☒ Other (specify): Starter Pack			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 06/15/2006 ***If yes, distribute minutes before filing meeting***	X			

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Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 08/09/2010 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

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RPM Filing Review

BLA 125057/232

Humira (adalimumab) – Adult UC

	4/8/11
Project Manager	**Date**
	4/8/11
Supervisor Concurence	**Date**

Reference ID: 3200370

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057Orig1s232

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 125057	NDA Supplement # BLA STN # 232	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: Humira Established/Proper Name: adalimumab Dosage Form: solution for injection (subcuetaneous)		Applicant: Abbott Laboratories Agent for Applicant (if applicable):
RPM: Kevin Bugin		Division: Division of Gastroenterology and Inborn Errors Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 09/28/2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None 11/21/2011 CR

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Reference ID: 3197501

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments: Orphan for Pediatric Indication, Includes a MedGuide

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3197501

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Reference ID: 3197501

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

Reference ID: 3197501

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	09/28/2012
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 09/28/2012; CR 11/21/2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Sep 2012
• Original applicant-proposed labeling	Jan 2011
• Example of class labeling, if applicable	Remicade Sep 2011

[3] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3197501

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Refer to PI
• Original applicant-proposed labeling	Refer to PI
• Example of class labeling, if applicable	Refer to PI
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	March 2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 04/08/2011 ☒ DMEPA 09/14/2012 ☒ DRISK 10/19/2011 ☒ DDMAC 09/10/2012; 10/31/2011 ☒ SEALD 09/11/2012 ☐ CSS ☒ Other reviews Patient Labeling 09/13/2012
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	04/08/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Pediatric indicaitno has oprhan designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	09/26/2012; 09/18/2012; 09/12/2012; 08/07/2012; 07/23/2012; 07/18/2012; 06/19/2012; 04/18/2012; 10/25/2011; 09/28/2011; 09/22/2011; 09/09/2011; 07/12/2011; 07/11/2011; 05/23/2011; 05/09/2011; 04/08/2011; 03/25/2011; 02/10/2011
❖ Internal memoranda, telecons, etc.	11/10/2011
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/23/2010
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	08/28/2012
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 09/28/2012; 11/21/2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 09/28/2012; 11/14/2011
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	N/A
• Clinical review(s) *(indicate date for each review)*	09/28/2012; 10/21/2011; 03/25/2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical Review - Section 3.3
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Reference ID: 3197501

❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 09/14/2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 09/27/2012;
Statistical Review(s) *(indicate date for each review)*	☐ None 09/24/2012; 10/28/2011; 03/26/2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 09/17/2012; 10/27/2011; 03/10/2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested

Reference ID: 3197501

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Review 11/16/2011 Memo 05/11/2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See DMA review, pg 2: 11/16/2011
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 11/18/2011 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3197501

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Reference ID: 3197501

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
10/01/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125057/232
Product Name:	Adalimumab
PMR/PMC Description:	**PMR #1** A study in inflammatory bowel disease (IBD) patients treated with Humira (adalimumab) in which you will bank tissue or blood samples (as appropriate) and then analyze them to identify genetic mutations and other biomarkers that predispose these patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/2013
	Study/Trial Completion:	09/2019
	Final Report Submission:	09/2020
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☒ Life-threatening condition
   ☒ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety signal
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with immunosuppressants including TNF-alpha-blockers for Inflammatory Bowel Disease. The disease is rare. Described cases have all been fatal. It is conceivable that polymorphism in genes involved in immunoregulatory functions predispose to this SAE. Whole genome sequencing or other suitable genomics studies conducted on patients who have been afflicted by HSTCL could identify those patients who are at risk for this SAE. However, given the rarity of HSTCL, enough high quality samples need to first be prospectively identified to be able to have enough power to detect relevant polymorphisms, if they indeed exist. This requires a study to bank samples for future evaluation to identify genetic mutations and other biomarkers that predispose inflammatory bowel disease (IBD) patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3197160

While cases of HSTCL are rare, they appear to be universally fatal. In addition, unlike most cancers, they have a predilection for younger individuals. Findings from studies conducted under this PMR could inform the safety labeling for adalimumab and potentially for the entire class of TNF-alpha blockers.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☒ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

At present, only the collection of high quality samples suitable for genetic/genomic analysis is required. Ultimately, the samples would be the material for a pharmacogenomic study.

Reference ID: 3197160

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☒ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125057/232
Product Name:	Adalimumab
PMR/PMC Description:	**PMR #2** A multi-center observational study of Humira (adalimumab) in adults with moderately to severely active ulcerative colitis treated in a routine clinical setting, to assess the long-term safety as measured by the incidence of opportunistic infections and malignancies. Long-term effectiveness should be assessed as a secondary goal. The proposed study should follow patients for a period of at least 10 years from time of enrollment in order to ascertain adverse events with longer latency periods such as malignancies. The primary analysis is to summarize safety data for patients on adalimumab and patients on non-biologic immunomodulator therapy. The study should be adequately sized to sufficiently detect a doubling of the risk of lymphoma events in each treatment group. A secondary analysis is to summarize safety data for patients on adalimumab and patients on the combination of adalimumab and non-biologic immunomodulator therapy. In addition, the study is to document and evaluate effects of withdrawal and re-treatment with adalimumab and "switching" with other tumor necrosis factor (TNF)-blockers or biologics.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2013
	Study/Trial Completion:	12/2027
	Final Report Submission:	12/2029
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety signal
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The incidence of the serious adverse event of interest, especially of certain malignancies, is low and data need to be accumulated over a10 year period.

Reference ID: 3197160

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The use of adalimumab and other TNF-alpha blockers and small molecule immunomodulators such as azathioprine, 6-mercaptupurine and methotrexate, has been associated with serious infections and malignancies. It is not clear whether TNF-alpha blockers alone or in combination contribute to these risks, and if, to what extent. Data from this PMR would provide important information relevant to the safety labeling of adalimumab and the class of TNF-alpha blockers.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3197160

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

Reference ID: 3197160

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	125057/232
Product Name:	Adalimumab (Humira)
PMR/PMC Description:	PMR #3: Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient blood samples collected from clinical studies and trials should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation final reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling.
Final Report Submission:	12/31/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Experience to date with this drug indicates that there is a sufficient level of safety with respect to the immunogenicity of the product. However, efficacy may also be affected by anti-drug antibodies, and the validated new assays are required for completion of PMR 4 (assessment of immunogenicity samples from study M10-223 and the trials conducted under PMR's 5, 6, and 7).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

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The current immunogenicity assays are not sufficiently sensitive when the study drug is present at high levels in the study sample. A portion of the immunogenicity samples that are collected during clinical studies may not be adequately assessed using the current assays. New immunogenicity assays are being developed to address this issue; validation studies will be performed to demonstrate the acceptability of the new assays.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assay validation studies will be performed to demonstrate that newly developed assays are specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of drug.

Reference ID: 3197160

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)

There are other PMR's for trials to study a higher induction dose (PMR #5) and to study dose escalation (PMR #6). Higher doses may be related to potential risk of developing severe adverse reactions. There are no data but it is anticipated that higher doses will result in improved efficacy, seen from exposure-response analysis. There is uncertainty regarding the benefit/risk at higher doses. At these doses, safety is not well established, and PK and immunogenicity is unknown as well. It will be important to have an assay that is capable of sensitively detecting AAA responses in the presence of drug.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Reference ID: 3197160

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(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 125057/232
Product Name: Humira (Adalimumab)

PMR/PMC Description: PMR #4: Utilizing a validated AAA assay as described in PMR #3 above, you should measure and analyze the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	06/2013
	Study/Trial Completion:	06/2018
	Final Report Submission:	12/2019
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☒ Only feasible to conduct post-approval
   ☒ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   The desired methodology is not available to conduct the assessment pre-approval because the sponsor is currently developing an improved assay.

   The immunogenicity profile of patients receiving Humira has not been adequately characterized because the current anti-adalimumab antibody assay is inadequate to evaluate most patient samples due to the drug interference in the assays for anti-adalimumab antibody (AAA) measurement.

   Currently, the sponsor screens all immunogenicity samples based on the adalimumab concentration and only conduct anti-adalimumab assay in samples containing less than 2 μg/mL concentration.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3197160

The goal of this post-marketing commitment is to assess the immunogenicity profile based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☒ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Measurement and analysis of the immunogenicity profile (utilizing a validated AAA assay as described in PMR #3) based on post-dose patient samples from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

Reference ID: 3197160

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Samples for immunogenicity testing are from completed study M10-223, the trial conducted under PMR #5, the trial conducted under PMR #6, and the trial conducted under PMC #7.

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☒ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125057/232
Product Name:	Adalimumab
PMR/PMC Description:	Conduct a trial in moderately to severely active ulcerative colitis patients to evaluate the safety of induction regimens of adalimumab at doses higher than 160/80 mg. In this trial, the efficacy of Humira (adalimumab) should also be assessed, both during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. In this trial, collecting samples for immunogenicity testing (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) and conducting analyses of the impact of immunogenicity on safety, pharmacokinetics, and efficacy is important. The protocol should be agreed upon by the agency prior to the initiation of the trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/2013
	Study/Trial Completion:	03/2018
	Final Report Submission:	03/2019
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This was not a pre-approval requirement because the primary endpoint for induction of clinical remission was met in two separate double blind randomized placebo controlled clinical trials. However, a modest treatment effect for induction of clinical remission (< 10%) was observed. Furthermore, the clinical remission rate increased with increasing adalimumab exposures without reaching a plateau in the pivotal trial. This raised a concern that the optimal dose of adalimumab for ulcerative colitis may not have been selected and that a higher dose may provide additional benefit. Therefore, a post-approval study to compare efficacy and safety of a 160/80 mg induction dosing regimen with higher induction dosing regimens will be valuable in the identification of the optimal dose for ulcerative colitis patients.

Reference ID: 3197160

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This recommendation is based on the exposure-response analysis conducted by the agency. This analysis indicates that an induction regimen with doses higher than 160/80 mg may provide additional benefit for inducing clinical remission. It is important to note that an induction dose higher than 160/80 mg has not been studied in the clinical development program. Therefore analysis of efficacy as well as safety will be important in this case.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3197160

A trial to compare efficacy and safety of a 160/80 mg induction dosing regimen with higher induction dosing regimens.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Assess the impact of immunogenicity on safety, pharmacokinetics, and efficacy.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☒ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

Reference ID: 3197160

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125057/232
Product Name:	Humira (Adalimumab)
PMR/PMC Description:	PMR #6: A safety and pharmacokinetic trial as a sub-study of the trial described in PMR #5 above to evaluate trough concentrations of adalimumab and antibody levels (utilizing a validated anti-adalimumab antibody assay as described in PMR #3 above) at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from dose escalation without increasing risk of serious adverse events. The protocol should be agreed upon by the agency prior to initiation of the trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/2013
	Study/Trial Completion:	03/2018
	Final Report Submission:	03/2019
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   At some point in the treatment of their disease, some UC patients may have loss of remission while on adalimumab therapy. Physicians may dose escalate by considering an option of increasing the dose or decreasing the dosing interval. The optimal strategy for doing so in a manner that does not increase the risk of serious adverse events remains unknown. Collection of trough samples for determination of adalimumab concentration prior to dose escalation will allow evaluation of a potential association between trough adalimumab concentrations and loss of remission.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3197160

Adalimumab doses higher than that currently approved may be associated with increased adverse events. In clinical practice, adalimumab doses may be increased in patients who have remitted on adalimumab but have lost remission during the course of their therapy. Determination of adalimumab concentration prior to dose escalation will allow evaluation of a potential association of low trough adalimumab concentrations with a loss of remission. The goal of this study is to evaluate whether trough concentrations at the time of loss of remission can be used to identify UC patients who have low adalimumab exposures and would benefit from a dose increase above that approved without increasing risk of serious adverse events.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3197160

A safety and pharmacokinetic trial to evaluate whether trough concentrations at the time of loss of remission can be used to identify UC patients who have low adalimumab exposures and would benefit from a dose increase above that approved without increasing risk of serious adverse events.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Evaluate the impact of immunogenicity on safety, pharmacokinetics, and efficacy.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☒ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

Reference ID: 3197160

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3197160

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	BLA 125057/232
Product Name:	Adalimumab
PMR/PMC Description:	**PMC #7:** Conduct a one-year, multi-center, randomized, double-blind placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed during induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect samples for immunogenicity testing (utilizing a validated AAA assay as described in PMR #3 above) and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2013
	Study/Trial Completion:	06/2018
	Final Report Submission:	12/2019
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a pediatric study which for which PREA (Pediatric Research Equity Act) requirements do not apply due to the orphan drug status of Humira. Therefore, this is a postmarketing commitment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3197160

The efficacy and safety of adalimumab for the indication of ulcerative colitis has not been established in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a one-year, multi-center, randomized, double-blind placebo controlled trial to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in pediatric patients 5 to 17 years of age with moderately to severely active ulcerative colitis. In this trial, the efficacy of adalimumab should be assessed with induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure response analysis.

Reference ID: 3197160

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3197160

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/s/

KEVIN B BUGIN
09/28/2012

ANIL K RAJPAL
09/28/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: September 28, 2012

Applicant Name: Abbott Laboratories, Inc
U.S. License #: 0043
STN(s): 125057/232
Product(s): Humira (adalimumab)
Short summary of application: Provides for the treatment of Ulcerative Colitis in Adults

---

FACILITY INFORMATION

[1]The regulations at 21 C F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Reference ID: 3196107

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number	Manufacturing Steps or Type of Testing	
Abbott Bioresearch Center	100 Research Drive Worcester, MA 01605 USA	3003684386	(b) (4)	Manufacture, testing, release and stability testing of drug substance	Inspected May 25 – June 1, 2010 and classified NAI. Comprehensive cGMP coverage of biotech drug substances was provided and deemed acceptable.
AbbVie Biotechnology Ltd.	Road No. 2, Km. 59.2 Barceloneta, PR 00617 USA	3004620772	N/A	Manufacture, testing, release and stability testing of drug substance	Inspected June 26 – July 12, 2012 and classified VAI. Comprehensive cGMP coverage of biotech drug substances was provided and deemed
(b) (4)					(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

AbbVie Biotechnology Ltd	Road No. 2, Km. 59.2 Barceloneta, PR 00617 USA	3004620772	N/A	Formulation, filling, visual inspection, release testing, and stability testing of unlabeled pre-filled syringes, testing of excipients, release of unlabeled pre-filled syringes filled at ABL for labeling and packaging in the US	Inspected June 26 – July 12, 2012 and classified VAI. Comprehensive cGMP coverage of drug product manufacturing operations was provided and deemed acceptable.

(b) (4)

[redacted] (b) (4)					
Abbott GmbH & Co. KG	Knollstrasse 67061 Ludwigshafen Germany	3002807401	N/A	Release testing of unlabeled pre-filled syringes and vials, stability testing of pre-filled syringes and vials, testing of excipients	Inspected May 8-15, 2009 and classified VAI. Laboratory operations were covered and are acceptable for this submission.
Abbott Biotechnology Deutschland GmbH	Max-Planck-Ring 2 65205 Wiesbaden Germany	N/A	N/A	Release of unlabeled pre-filled syringes and vials filled [redacted] (b) (4) for labeling and packaging in the US; release of labeled product for the US if labeled and packaged [redacted] (b) (4)	This site has no FDA inspectional history. OMPQ/DIDQ has obtained information from the German regulatory authorities (ZLG) and determined that this site was inspected on January 19th, 2012 and found to be in compliance with CGMP as defined by ZLG. This inspection covered warehousing operations and visual inspection of sterile parenterals. CDER is planning an inspection of this facility for early October 2012. Based on the risk associated with the operations presented, the ZLG assessment, and the planned expedited surveillance inspection of this facility, NDMAB finds this site acceptable for the purposes of this supplement at this time.
Abbott Laboratories	100 Abbott Park Rd. Abbott Park, IL 60064 - USA	1415939	N/A	Labeling and packaging of vials and pre-filled syringes, release of labeled product	Inspected July 11-15, 2011 and classified VAI. Packaging and labeling operations for sterile drug products were covered and are acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions to prevent approval of STN 125057/232 at this time.

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/s/

MARISA E STOCK
09/27/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Post-marketing Requirements and Commitments - September 18, 2012
Date:	Tuesday, September 18, 2012 4:37:18 PM

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

Below please find a list of 6 post-marketing requirements and commitments. Please note that we have not finalized the wording for PMR #2. We have proposed dates for these PMR/PMCs where we thought it reasonable for us to do so. Please review these dates and provide dates for any goals not yet defined.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Post-marketing Requirements and Commitments

PMR #1
A study to bank samples for future evaluation to identify genetic mutations and other biomarkers that predispose inflammatory bowel disease (IBD) patients to developing Hepatosplenic T-Cell Lymphoma (HSTCL).

Final Protocol Submission:	06/2013
Study Completion:	06/2019
Final Report Submission:	06/2020

PMR #2
Patient registry (wording to be finalized and sent at a later time).

PMR #3
A safety and pharmacokinetic trial as a substudy of the registry described in PMR #2 to evaluate trough concentrations and antibody levels at the time of loss of clinical remission in patients whose physicians plan to escalate the dose (e.g., decrease the dosing interval to weekly or increase the dosage) in response to loss of remission. Trough concentrations will be evaluated to determine whether patients who have low adalimumab exposures benefit from an escalation of the dose without increasing risk of serious adverse events.

Final Protocol Submission:	06/2013
Trial Completion:	12/2020

Final Report Submission: 12/2021

PMC#4

Conduct a trial to evaluate efficacy and safety of induction regimens at doses higher than 160/80 mg. In this trial, the efficacy of adalimumab should be assessed with induction treatment as well as during continued treatment after induction, and pharmacokinetic measurements should be conducted for exposure-response analysis. Also, collect immunogenicity samples and conduct analyses of the impact of immunogenicity on pharmacokinetics, efficacy and safety. The protocol should be agreed upon by the agency prior to the initiation of the trial.

Final Protocol Submission: 06/2013
Study/Trial Completion: 06/2016
Final Report Submission: 06/2017

PMC#5

Develop, qualify, and implement improved validated anti-adalimumab antibody (AAA) assays with reduced sensitivity to product interference. Until assays have been developed and validated, patient samples collected from clinic studies should be banked under appropriate storage conditions. You will provide assay SOPs, validation protocols, and validation study reports that include data demonstrating that the assay is specific, sensitive and reproducible, and capable of sensitively detecting AAA responses in the presence of adalimumab levels that are expected to be present at the time of patient sampling as a prior approval supplement (PAS) by XX, 20XX.

Final Report Submission: Please provide a goal date. MM/YYYY

PMC#6

Utilizing a validated AAA assay as described in PMC #5 above, you should assess the immunogenicity profile based on post-dose patient samples from the study conducted under PMR #2 and the trial conducted under PMC #4.

Final Protocol Submission: 06/2013
Study/Trial Completion: 06/2016
Final Report Submission: 06/2017

_____

Kevin Bugin, MS, RAC
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

"Opportunities are seldom labeled."
- John A. Shedd

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/s/

KEVIN B BUGIN
09/18/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira UC - Labeling Comments - September 12, 2012
Date:	Wednesday, September 12, 2012 8:24:21 AM
Attachments:	Humira PI FDA Redline_12Sep2012.doc

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

Please find attached an annotated WORD document containing FDA's revisions to the proposed labeling for this supplement. Revisions are throughout the label. DMEPA continues to review the revised carton labeling and if/when comments are available, we will send these under a separate communication.

We are continuing to work on post marketing commitments and requirements. These will also be sent under a separate communication.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302
"Opportunities are seldom labeled."
- John A. Shedd

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/s/

KEVIN B BUGIN
09/12/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
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1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: September 28, 2012

Applicant Name: Abbott Laboratories, Inc
U.S. License #: 0043
STN(s): 125057/232
Product(s): Humira (adalimumab)
Short summary of application: Provides for the treatment of Ulcerative Colitis in Adults

---

FACILITY INFORMATION

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number	Manufacturing Steps or Type of Testing
Abbott Bioresearch Center	100 Research Drive Worcester, MA 01605 USA	3003684386	(b) (4)	Manufacture, testing, release and stability testing of drug substance
AbbVie Biotechnology Ltd.	Road No. 2, Km. 59.2 Barceloneta, PR 00617 USA	3004620772	N/A	Manufacture, testing, release and stability testing of drug substance

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3191069

(b) (4)

AbbVie Biotechnology Ltd	Road No. 2, Km. 59.2 Barceloneta, PR 00617 USA	3004620772	N/A	Formulation, filling, visual inspection, release testing, and stability testing of unlabeled pre-filled syringes, testing of excipients, release of unlabeled pre-filled syringes filled at ABL for labeling and packaging in the US

(b) (4)

Abbott GmbH & Co. KG	Knollstrasse 67061 Ludwigshafen Germany	3002807401	N/A	Release testing of unlabeled pre-filled syringes and vials, stability testing of pre-filled syringes and vials, testing of excipients
Abbott Biotechnology Deutschland GmbH	Max-Planck-Ring 2 65205 Wiesbaden Germany	N/A	N/A	Release of unlabeled pre-filled syringes and vials filled (b) (4) for labeling and packaging in the US; release of labeled product for the US if labeled and packaged (b) (4)
Abbott Laboratories	100 Abbott Park Rd. Abbott Park, IL 60064 - USA	1415939	N/A	Labeling and packaging of vials and pre-filled syringes, release of labeled product

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/s/

KEVIN B BUGIN
09/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE/DEPI	Kevin Bugin, Regulatory Health Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-2302

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
09/13/2013		BLA 125057/232	sBLA	03/30/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Humira (adalimumab)	Standard	Biologic	09/20/2012

NAME OF FIRM: Abbott Labs

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

S/TATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We have a supplemental biologics application under review for Humira (adalimumab) for the treatment of ulcerative colitis and it is nearing approval in a couple of weeks. September 28 to be exact.

The team has decided that there should be a post marketing commitment to conduct a safety registry. We are hoping that your group can assist us with the calculations and any other suggestions regarding the this PMC.

Here is what the applicant has proposed and a link to the eCTD. If you need further information please let me know or you can contact the medical team leader, Anil Rajpal.

Protocol:
\\cber-fs3\m\eCTD_Submissions\STN125057\\0134\m5\53-clin-stud-rep\536-postmark-exp\p11-282\p11282-protocol-original.pdf
BLA:

\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx	
SIGNATURE OF REQUESTER **Kevin Bugin**	METHOD OF DELIVERY (Check one) ☒ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KEVIN B BUGIN
09/13/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira UC - Labeling Comments - September 12, 2012
Date:	Wednesday, September 12, 2012 8:24:21 AM
Attachments:	Humira PI FDA Redline 12Sep2012.doc

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

Please find attached an annotated WORD document containing FDA's revisions to the proposed labeling for this supplement. Revisions are throughout the label. DMEPA continues to review the revised carton labeling and if/when comments are available, we will send these under a separate communication.

We are continuing to work on post marketing commitments and requirements. These will also be sent under a separate communication.

If you have any questions, please do not hesitate to contact me.

Regards,

_____

Kevin Bugin, MS, RAC
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
FDA\CDER
301-796-2302

"Opportunities are seldom labeled."
- John A. Shedd

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/s/

KEVIN B BUGIN
09/12/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira - Clinical Pharmacology Information Request - August 07, 2012
Date:	Tuesday, August 07, 2012 11:35:40 AM

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

We are reviewing the clinical pharmacology sections of your supplemental BLA and have the following comments and questions:

1. We note that in the exposure-response plots displayed in Figure 6 and Figure 8 of your resubmission (dated March 30, 2012), it appears that the total number of subjects with measured adalimumab concentrations at Week 8 is 239. In the PK dataset submitted in the original submission (pk-dataset.xpt), there are only 220 subjects with measured adalimumab concentrations at Week 8. Of these 220 subjects, concentrations for 7 subjects were below the limit of quantitation. Provide an explanation for the apparent discrepancy between the numbers.

2. In your Advisory Committee Briefing Document, you have presented new exposure-response analyses using an Emax logistic regression model. This analysis was not submitted to the Agency previously and was therefore could not be reviewed. In the new analysis, you conclude that "efficacy approaches a plateau at the upper concentration quartiles of the studied adalimumab dose." First, we find this to be a circular argument because you are apparently fixing the Emax parameter in your model based on data from Study M06-827. Second, this statement appears to be in contrast with your statement on page 105 of the resubmission that "an increase in induction dose may increase the overall efficacy at Week 8." Therefore, we believe that the Emax model may not be appropriate for describing the exposure-response data for the induction phase. Based on the analysis conducted by the FDA, an increase in adalimumab concentration is associated with an increase in clinical remission rate at Week 8. Furthermore, this relationship does not reach a plateau over the range of concentrations observed at the proposed induction dose which suggest a higher induction dose may provide a higher remission rate.

If you have any questions, please do not hesitate to contact me.

Regards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave

Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904
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If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

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/s/

KEVIN B BUGIN
08/07/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira - Statistics Information Request - July 23, 2012
Date:	Monday, July 23, 2012 11:23:52 AM

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

Further reference is made to the official response document to the November 21, 2011, complete response letter and the Integrated Summary of Safety (ISS, R&D/10/238). We request that you address the following two points by August 1, 2012.

1. In the Net Efficacy Adjusted for Risk (NEAR) Analysis (page 70-72) analysis using the response per MAYO score at week 8 as the efficacy endpoint, 180/468 and 241/471 patients in the placebo and ADA 160/80/40 group, respectively, had a response (Tables 1__4.1 to 1__4.3). This analysis used the IAS-E analysis set. In Table 5 (page 49) using the same analysis set and endpoint, 176/468 and 240/470 patients in the placebo and ADA 160/80/40 group, respectively, are reported having a response.

   Compared to findings presented in Table 5, clarify the following for the NEAR analysis
   a. Why the placebo group has an additional 4 patients with a response.
   b. Why the ADA 160/80/40 group has an extra patient (which had a response).

   If the data used for the NEAR analysis are incorrect, provide revised estimates using the corrected data along with explanation.

2. The definition of the Induction Set in the official response document is not consistent with the definition in the ISS, as reported in the official response document. On page 60 of the official response document, the Induction Set is defined as

   > The Induction Set (as defined in the ISS [R&D/10/238]) included DB data between Weeks 0 and 8 in Study M06-826 and DB data between Weeks 0 and 52 in Study M06-827 for all subjects who received at least one dose of randomized DB adalimumab or placebo.

   In the ISS (Table 2, page 118), the Induction Set is defined for studies M06-826 and M06-827 as

   > Double-blind data between Week 0 and Week 8 from all subjects who received at least one dose of randomized double-blind adalimumab or placebo.

Please clarify why the definition of Induction Set in the Official Response document differs from the ISS.

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Please consider the environment before you print.

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/s/

KEVIN B BUGIN
07/23/2012

From:	Bugin, Kevin
To:	Bonnie W Kain
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira - Statistics Information Request - July 18, 2012
Date:	Wednesday, July 18, 2012 12:32:22 PM

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

Regarding your response to the November 21, 2011, complete response letter, please provide the following material by July 20, 2012:

- Program code to replicate results in Table 13 (page 62), Table 14 (page 64), and Table 15 (page 65).
- Program code to results for Tables 1_4.1 through 1_4.6 (page 166-171)

If you have any questions, please do not hesitate to contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

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/s/

KEVIN B BUGIN
07/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: DBVII/Safety Stats

FROM:
Kevin Bugin, Regulatory Health Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-2302

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/17/2012		BLA 125057/232	Class II Resubmission	03/30/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Humira (adalimumab)	Standard	Biologic	08/282012

NAME OF FIRM: Abbott Labs

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
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- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

EDR link to submission:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx

The eRoom link for the application is:
http://eroom fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2bf0c

The clinical reviewer has the question below:

•The sponsor did not conduct any new clinical studies but performed a number of post-hoc analyses including a "composite measure of benefit risk" (section 2.1.1.2.8). We are concerned that this approach obscures more than it reveals and that especially the use of a single statistic called Net Efficacy Adjusted For Risk (NEAR) is problematic because it condenses study efficacy data with incomplete safety information. DGIEP requests that you review the methodology employed and give us an opinion whether the sponsor's composite measure of benefit risk does or does not support approvability of the drug.

The sponsor discusses "Composite Measures of Benefit/Risk" in Pages 61 to 68 of the document "agency-response-2011-nov-21-pub.pdf". This document is available at the following link: \\cber-fs3\m\eCTD_Submissions\STN125057\0134\m1\us.
(The link to the sponsor's resubmission is: \\cber-fs3\m\eCTD_Submissions\STN125057\0134.) Datasets can also be found here.

Our current draft briefing document and questions to the AC are at the following links:
•Draft AC Questions: http://eroom fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2ccfc
•Draft Briefing Document: http://eroom fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2ccf8

Note that we discuss All-Cause and UC-related Hospitalizations in section 1.3.7.5 of the draft briefing document (pages 18-20).

SIGNATURE OF REQUESTER Kevin Bugin	METHOD OF DELIVERY (Check one) ☒ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KEVIN B BUGIN
07/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE/DMEPA

FROM:
Kevin Bugin, Regulatory Health Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-2302

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/12/2012		BLA 125057/232	MedGuide/PI /Carton/Container	03/30/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Humira (adalimumab)	Standard	Biologic	09/15/2012

NAME OF FIRM: Abbott Labs

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Sponsor has submitted data to support labeling revisions to include the treatment of Ulcerative Colitis.
The sponsor has modified the PI and the MedGuide to add the additional information to support this use. The MedGuide was part of the original application's REMS.

EDR link to submission:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx

The eRoom link for the application is:
http://eroom fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2bf0c

Meeting	Date	Location
Labeling Planning Meeting	Jul 11, 3 PM	CDER WO 5313
Labeling Meeting 1	Aug 21, 9 AM	CDER WO 5313
Labeling Meeting 2	Sep 06, 1 PM	CDER WO 5313
Labeling Meeting 3	Sep 12, 3 PM	CDER WO 5313

Labeling Meeting 4	Sep 19, 10 AM	CDER WO 5313

SIGNATURE OF REQUESTER Kevin Bugin	METHOD OF DELIVERY (Check one) ☒ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KEVIN B BUGIN
07/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE/DRISK

FROM:
Kevin Bugin, Regulatory Health Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-2302

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
07/12/2012		BLA 125057/232	MedGuide/PI	03/30/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Humira (adalimumab)	Standard	Biologic	09/15/2012

NAME OF FIRM: Abbott Labs

REASON FOR REQUEST

I. GENERAL

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- ☐ PROGRESS REPORT
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- ☐ ADVERSE REACTION REPORT
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- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
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- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
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III. BIOPHARMACEUTICS

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V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Sponsor has submitted data to support labeling revisions to include the treatment of Ulcerative Colitis.
The sponsor has modified the PI and the MedGuide to add the additional information to support this use. The MedGuide was part of the original application's REMS.

EDR link to submission:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx

The eRoom link for the application is:
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Meeting	Date	Location
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SIGNATURE OF REQUESTER Kevin Bugin	METHOD OF DELIVERY (Check one) ☒ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

KEVIN B BUGIN
07/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Kevin Bugin/RPM, ODEIII/DGIEP, 6-2302

REQUEST DATE:
07/12/2012

NDA/BLA NO.:
BLA 125057/232

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

sBLA – Med Guide

NAME OF DRUG:

Humira (adalimumab)

PRIORITY CONSIDERATION:
Priority

CLASSIFICATION OF DRUG:
Anti TNF

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

09/19/2012

SPONSOR:

Abbott Labs

PDUFA Date: 09/28/2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☒ ORIGINAL NDA/BLA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☒ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx

eRoom link to labeling, when available:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2bf0c

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Meeting	Date	Location
Labeling Meeting 1	Aug 21, 9 AM	CDER WO 5313
Labeling Meeting 2	Sep 06, 1 PM	CDER WO 5313
Labeling Meeting 3	Sep 12, 3 PM	CDER WO 5313
Labeling Meeting 4	Sep 19, 10 AM	CDER WO 5313

SIGNATURE OF REQUESTER
Kevin Bugin

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

KEVIN B BUGIN
07/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Kevin Bugin, Regulatory Health Project Manager, Office of Drug Evaluation III, Division of Gastroenterology Products, 301-796-2302

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
07/12/2012		125057/232	(PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Humira (adalimumab)	Standard Review	Biologic	(Generally 1 week before the wrap-up meeting) 09/15/2012

NAME OF FIRM:

Abbott Laboratories

PDUFA Date: 09/28/2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☒ CARTON/CONTAINER LABELING
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☒EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:
\\cber-fs3\m\eCTD_Submissions\STN125057\125057.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling will be placed in the eRoom at: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_2bf0c

Meeting	Date	Location
Labeling Planning Meeting	Jul 11, 3 PM	CDER WO 5313
Labeling Meeting 1	Aug 21, 9 AM	CDER WO 5313
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Labeling Meeting 4	Sep 19, 10 AM	CDER WO 5313

SIGNATURE OF REQUESTER

Kevin Bugin	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

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/s/

KEVIN B BUGIN
07/12/2012

From:	Bugin, Kevin
To:	"Bonnie W Kain"
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 Humira - Clinical Information Request - June 19, 2012
Date:	Tuesday, June 19, 2012 12:38:00 PM

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, and its resubmission received March 30, 2012, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the clinical sections of your supplement, we have the following comments and requests for information:

1. The report "Adalimumab Risk of Hospitalization and Colectomy R&D/12/280" presents post-hoc analyses of pooled data derived from the 160/80/40 mg and placebo arms of Study 826 (ITT-E population) and Study 827 (ITT population). However, analyses are not presented for each study separately, for the low dose (80/40 mg) arm of Study 826, and for the ITT-A3 population of Study 826.

   Provide analyses of the same outcomes presented in the report "Adalimumab Risk of Hospitalization and Colectomy R&D/12/280" for the following study populations and treatment groups:
   - Study 826 (ITT-E population): 160/80/40 mg, 80/40 mg, and placebo arms
   - Study 826 (ITT-A3 population): 160/80/40 mg, 80/40 mg, and placebo arms
   - Study 827 (ITT population): 160/80/40 mg and placebo arms

2. Provide a brief summary (limited to a few pages) of exposure data (number of patients exposed, dose, and duration of exposure) from clinical trials (including trials for other indications) that used higher doses than those in Studies 826 and 827.

If you have any questions, please do not hesitate contact me.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302
F-301-796-9904

++
If you are not the intended recipient you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2302 or by return e-mail.

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Please consider the environment before you print.

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/s/

KEVIN B BUGIN
06/19/2012

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: September 30, 2012

Applicant Name: Abbott Laboratories, Inc
U.S. License #: 0043
STN(s): 125057/232
Product(s): Humira (adalimumab)
Short summary of application: Provides for the treatment of Ulcerative Colitis in Adults

---

FACILITY INFORMATION

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number	Manufacturing Steps or Type of Testing	Compliance Status
Abbott Bioresearch Center	100 Research Drive Worcester, MA 01605 USA	3003684386	(b) (4)	Manufacture, testing, release and stability testing of drug substance	Inspected May 25-June 1, 2010 and classified NAI. Adalimumab drug substance manufacturing was covered and is acceptable.

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Reference ID: 3137873

Abbott Biotechnology Ltd.	Road No. 2, Km. 59.2 Barceloneta, PR 00617 Puerto Rico	3004620772	N/A	Manufacture, testing, release and stability testing of drug substance	Inspected September 12-20, 2011 and classified VAI. Adalimumab drug substance manufacturing was covered and is acceptable

(b) (4)

(b) (4)

Abbott GmbH & Co. KG	Knollstrasse 67061 Ludwigshafen Germany	3002807401	Release testing of unlabeled pre-filled syringes and vials, stability testing of pre-filled syringes and vials, testing of excipients	Inspected 5/8/09-5/15/09 and classified VAI. The CTL profile was covered and is acceptable.

Abbott Biotechnology Deutschland GmbH	Max-Planck-Ring 2 65205 Wiesbaden Germany	3002809144	Release of unlabeled pre-filled syringes and vials for labeling and packaging in the US; release of labeled product for the US if labeled and packaged (b) (4)	Inspected February 6-9, 2012 and classified NAI. Device QSIT coverage was provided, however DGMPA has determined that this site is acceptable for the responsibilities stated in this submission
Abbott Laboratories	100 Abbott Park Rd. Abbott Park, IL 60064 - USA	1415939	Labeling and packaging of vials and pre-filled syringes, release of labeled product	Inspected July 11-15, 2011 and classified VAI. Packaging and labeling operations for SVS were covered and are acceptable.
(b) (4)				
Abbott Biotechnology Limited	Road No. 2, Km 59.2 Barceloneta, PR	3004620772	Formulation, filling, visual inspection, release, stability	Inspected September 12-20, 2011 and classified VAI. The TRP profile was covered and is acceptable.

OVERALL RECOMMENDATION

The Division of Good Manufacturing Practice Assessment has completed its review and evaluation of the TB-EER below. Please see attached form for details regarding the each facility's compliance status. DGMPA's compliance recommendation remains withhold due to the ongoing compliance action against (b) (4) Please resubmit this TB-EER prior to taking action on this submission for a final compliance recommendation.

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/s/

MARISA E STOCK
05/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/232

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

We have received your March 30, 2012, resubmission to your supplement to your biologics license application for Humira (adalimumab) on March 30, 2012.

The resubmission contains additional clinical, labeling, facility inspections, immunogenicity, statistical data and safety updates that you submitted in response to our November 21, 2011, complete response letter.

We consider this a complete, class 2 response to our November 21, 2011, action letter. Therefore, the user fee goal date is September, 28, 2012.

If you have any questions, call me, at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KEVIN B BUGIN
04/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125057/232

DEFICIENCIES PRECLUDE DISCUSSION
October 25, 2011

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 25, 2011, received January 25, 2011, submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We also refer to the target date of October 26, 2011, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your supplemental application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

/R. Wesley Ishihara/
R. Wesley Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REVIEW DEFERRAL MEMO

Date:	October 19, 2011
To:	Donna Griebel, MD, Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** Barbara Fuller, RN, MSN, CWOCN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Risk Management**
Subject:	Review Deferred: Medication Guide
Drug Name(s):	HUMIRA (adalimumab) Injection, Solution for Subcutaneous use
Application Type/Number:	BLA 125057
Submission Number:	232
Applicant/Sponsor:	Abbott Laboratories
OSE RCM #:	2011-1063

This memorandum documents the deferral of our review of HUMIRA (adalimumab). On March 24, 2011, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that OSE review the proposed Medication Guide (MG) and the Instructions for Use (IFU) for HUMIRA (adalimumab).

Due to outstanding clinical deficiencies, the Division of Gastroenterology and Inborn Errors Products plans to issue a Complete Response (CR) letter. Therefore, DRISK defers comment on the Applicant's Medication Guide at this time. A final review will be performed after the Applicant submits a Complete Response to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

CC List:

DGIEP
Donna Griebel
Kevin Bugin
Andrew Mulberg
Aisha Johnson
Anil Rajpal
Fang Cai
Richard Ishihara

OSE:
Barbara Fuller
LaShawn Griffiths
Nitin Patel

DDMAC
Kendra Jones
Kathleen Klemm
Roberta Szydlo

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion
Division of Direct-to-Consumer Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 13, 2011

To: Kevin Bugin, MS, RAC, Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Kathleen Klemm, Pharm.D., Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Twyla Thompson, Pharm.D., Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
OPDP

CC: Lisa Hubbard, R.Ph., Professional Group Leader
DPP/OPDP
Shefali Doshi, M.D., DTC Group Leader
DDTCP/OPDP

Subject: BLA 125057/232 HUMIRA (adalimumab) Injection, Solution for Subcutaneous use [Humira]
OPDP Labeling Consult Response

We acknowledge receipt of your February 11, 2011, consult request for the proposed Package Insert, Medication Guide, and Carton/Container Labeling for Humira. OPDP was notified by DGIEP on October 4, 2011, that the Review Division plans to issue a Complete Response and will not be providing labeling comments. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DGIEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.
If you have any questions on the Package Insert or Carton/Container Labeling, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions concerning the Medication Guide, please contact Twyla Thompson at 301.796.4294 or Twyla.Thompson@fda.hhs.gov.

Reference ID: 3200370

Bugin, Kevin

n:	Bugin, Kevin
.it:	Wednesday, September 28, 2011 1:39 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Clinical Pharmacology Information Request - September 28, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

In your submission (Module 5.3.5.1.1 CSR analytical appendix report, Study M06-827_PK page 5), you stated that "All samples were analyzed using the final analytical method described in the validation report ANA09-004: Determination of Adalimumab in Human serum via Double-Antigen- Bridging-ELISA (b) (4) R&D09/341". However, we could not locate the validation report ANA 09-004 in your submission. Please submit a copy for our electronic file and confirm if this final analytical method was submitted under the original BLA or previous supplements for adalimumab.

'ou have any questions, please do not hesitate to contact me.

.,nd regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

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This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Please consider the environment before you print.

Bugin, Kevin

n:	Bugin, Kevin
.it:	Thursday, September 22, 2011 2:07 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Clinical Pharmacology Request - September 22, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

We have the following clinical pharmacology comments and requests for information:

1. We acknowledge that you provided in your response to Agency's IR letter, dated July 11, 2011, two estimated AAA+ rates using different denominators. Both estimates were based on the subset of subjects who completed the treatment which you argued to be the appropriate population.

   The first calculated AAA+ rate is 22.6% (7/31) using the number of subjects who have serum concentrations <2 µg/mL as the denominator. In contrast, the second calculated AAA+ rate is 4.2% (7/165) using the number of subjects who have were assigned to the adalimumab treatment arm and have eligible immunogenicity samples.

   We note that your position is in favor of the immunogenicity rate of 4.2% estimated by the second method because you believe that AAA+ rate calculated based upon a denominator of only subjects with serum adalimumab concentrations < 2 µg/mL overstates the proportion of subjects who are AAA+ by ignoring the large proportion of patients that are AAA- in the group with serum adalimumab concentrations ≥ 2 µg/mL.

   We have listed our comments to your response below.

   (1) We do not agree with you on the choice of the subset of subjects who completed the treatment (i.e., N=165) in the estimation of immunogenicity rate.

   The generally accepted definition of an anti-drug antibody positive (ADA+) subject is a subject who developed anti-drug antibody after treatment and at any time during the study. Therefore, the pool of subjects for the AAA+ calculation should be the 360 subjects that had evaluable AAA data, not the 165 subjects who completed the study on the regimen.

   (2) We argue that the second method of calculation inappropriately assumes AAA- in all subjects with adalimumab concentration ≥ 2 µg/mL because there is no data to support this assumption. As such, this method very likely under-estimates the immunogenicity (ADA+) rate. The Agency believes that the ADA+ rate should be calculated using the number of subjects who have serum adalimumab concentrations < 2 µg/mL as the denominator. The following provides our reasoning.

By definition, the % of ADA+ subjects = $\frac{ADA+}{(ADA+)+(ADA-)}$

In the case of adalimumab, a majority (>80%, 134 of 165) of subjects did not have AAA evaluated because of the anticipated drug interference as the serum adalimumab concentration was ≥ 2µg/mL. By estimating ADA+ as 7/165, the ·ond method essentially assumes AAA- for these subjects without experimental data to support it. We argue that the ɔability is extremely low for this assumption to be true. For instance if the true AAA+ rate were 4.2% and AAA- rate were 95.8%, the probability of all 134 subjects being AAA- is <0.005, calculated as $(0.958)^{134}$. This probability is much lower if the true AAA+ rate were 22.5%.

Reference ID: 3200370

(3) We do not agree with your statement that the first method of calculation ignores a large proportion of patients that are AAA- in the group with serum adalimumab concentrations ≥ 2 µg/mL. Instead, this method assumes that some of the subjects who were not evaluated for AAA are AAA+ and others are AAA-. Implicitly, it assumes that the distribution of AAA+ vs. AAA– within the subset of 134 subjects who had adalimumab concentration ³ 2 µg/mL is the same as those with confirmed AAA+ and AAA-.

Mathematically, this can be demonstrated as follows. Among subjects (N=134) with no AAA data because adalimumab concentration is ³ 2 µg/mL, this method would lead to an estimate that 30 subjects are AAA+ and 104 subjects are AAA- given an immunogenicity rate of 22.5%. The overall data from 31 subjects with confirmed AAA data (7 AAA+ and 24 AAA-) and 134 subjects with the projected AAA status (30 AAA+ and 104 AAA-), the overall count of AAA+ is 37 which represent approximately 22.5% of all 165 subjects.

The Agency requests that you recalculate the ADA+ rate based on all subjects who have evaluable AAA data (i.e., N=360) and use the number of subjects who have serum concentrations below 2 µg/mL as the denominator. The recalculated rate should be reflected in your proposed labeling.

2. Adalimumab is a known modulator of cytokines (e.g., IL-6 and TNF-α). These cytokines are known to modulate cytochrome P450 (CYP) activity in humans and alter the metabolism of CYP substrates [1, 2]. Patients with inflammatory diseases have elevated cytokines levels and suppressed CYP enzyme activity [3]. After treatment of adalimumab the cytokine levels decreases in these patients which may restore CYP activities to higher levels leading to increased metabolism of drugs that are CYP substrates.

Please update the adalimumab labeling Section 7.1 Drug interactions and Section 12.3 Pharmacokinetics to reflect that treatment with adalimumab can have impact on CYP enzymes and the potential of drug-drug interaction (DDI) between adalimumab and CYP substrates. Additionally, we recommend that you develop a strategy to quantitatively evaluate potential DDI which may include conducting prospective clinical studies.

References:

(1) Huang SM, Zhao H, Lee JI, Reynolds K, Zhang L, Temple R, et al. Therapeutic protein-drug interactions and implications for drug development. Clin Pharmacol Ther 2010 Apr;87(4):497-503.

Lee JI, Zhang L, Men AY, Kenna LA, Huang SM. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. Clin Pharmacokinet 2010 May 1;49(5):295-310.

(3) Morgan ET, Goralski KB, Piquette-Miller M, Renton KW,et al. Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. Drug Metabolism and Disposition 2008 Feb; 36(2):205-16

Please let me know if you have any questions.

Regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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ü Please consider the environment before you print.

Bugin, Kevin

m:	Bugin, Kevin
t:	Friday, September 09, 2011 8:08 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Statistics and Clinical Information Request - September 09, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the statistical and clinical sections of your supplement, we have the following comments and requests for information:

1. For Study 827, please provide primary efficacy results for the primary and first ranked secondary efficacy variables (Remission at Week 8, Remission at Week 52, and Remission at Weeks 8 AND 52) for the population of patients in the ITT set COMBINED with the 24 patients excluded for site violations. This set should include 260 placebo patients and 258 Humira patients. Please provide the efficacy results using the same stratification used for the primary efficacy analysis of the ITT set submitted in your original submission.

2. Perform an analysis of remission at Week 8 for the ITT-A3 dataset to exclude all subjects with protocol deviations during the double blind (DB) period throughout Week 8 given in Table 7 with no imputation for missing data for Study M06-826.

3. Perform an analysis of remission at Week 8, at Week 52, and at Week 8 and Week 52 for the ITT analysis dataset to exclude all subjects with protocol deviations during the DB period given in Table 6 with no imputation for missing data for Study M06-827.

4. Perform analyses of remission for Study M06-826 (at Week 8), and for Study M06-827 (at Week 8, at Week 52, and at Week 8 and Week 52) using the following new FDA definition of remission:

   Total Mayo score ≤ 2, with rectal bleeding subscore = 0 (no bleeding), endoscopy subscore = 0 (e.g., no friability), and no individual subscore > 1.

5. Perform observed case, complete case, and multiple imputation analyses for the new FDA definition of remission for Study M06-826 (at Week 8) and for Study M06-827 (at Week 8, at Week 52, and at Week 8 and Week 52).

6. In your response to information request dated May 27, 2011, it was found that the number of subjects with observed Mayo score at Week 8 (for the complete case analysis), at Week 52 (for the observed case and complete case analyses), and at Week 8 and Week 52 (for the observed case and the complete case analyses) for Study M06-827 appeared to be too small and incorrect. Please verify the numbers you provided.

7. Explain the reason that subjects in Study M06-826 that were included in the observed case analysis (for remission at Week 8) were excluded in the complete case analysis (for remission at Week 8), and provide information (such as subject identification number, baseline and demographic characteristics data, and efficacy data, last week completed, complete status) for these subjects.

you have any questions, please do not hesitate to contact me.

Reference ID: 3200370

nd regards,
evin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

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Please consider the environment before you print.

Bugin, Kevin

m: Bugin, Kevin
.it: Tuesday, July 12, 2011 3:34 PM
To: 'Bonnie W Kain'
Cc: Bugin, Kevin
Subject: BLA 125057/232 - Clinical/Pharmacometrics Information Request - July 12, 2011

Follow Up Flag: Follow up
Flag Status: Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the clinical and pharmacometrics information, we have the following comments:

Pharmacometrics
Please provide the dataset that has the time for patients switching to open label adalimumab for the study M06-827. If this time variable is captured in some dataset in your submission, please point us to the proper dataset and variable. Otherwise, this time variable should be reported in units of "study day from first dose date", and in units of "mapped week from first dose, num" with the corresponding variable names DB_QSDY and DB_WEEK, respectively.

:ddition, also provide the time for patients escalating to every week adalimumab in study M06-827. If this time variable captured in some dataset in your submission, please point us to the proper dataset and variable. Otherwise, this time variable should be reported in units of "study day from first dose date", and in units of "mapped week from first dose, num" with corresponding variable names ESC_QSDY and ESC_WEEK, respectively.

The following table gives an example of a layout for the dummy dataset:

SUBJID	DB_QSDY	DB_WEEK	ESC_QSDY	ESC_WEEK
00000	...	...	...	...
00001	...	...	...	...
00002	...	...	...	...

We acknowledge that SF36.xpt contains the variables DB and EOW which provide the double-blind and dose-escalation information at weeks 0, 4, 8, 20, 32, and 52. However, we would like to know in more detail when the open-label and dose escalation decisions were made since the patient could switch to open label adalimumab at the beginning of week 12. For example, if a patient is double-blind at week 20 and open-label at week 32, we would like to know when the decision was made during the 12-week interval between those two observations.

The requested data should be submitted in the form of a SAS transport (.xpt) file along with the define file.

Clinical
1. Please provide an efficacy analysis using the following efficacy (induction and maintenance) analysis sets:
   a) (Study 826) All patients on Humira 160/80/40 enrolled prior to Amendment 3.
   b) (Study 827) The 24 patients removed for site violations

2. Please submit an updated ISS. The submitted ISS has a data cut-off date of 31 December 2009. This date is more than 18 months ago and nearly 12 months prior to the date of the current submission.

If you have any questions, please do not hesitate to contact me.

Reference ID: 3200370

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
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US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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Please consider the environment before you print.

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
sion of Gastroenterology and Inborn Errors Products
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Silver Spring, MD 20993-002
P-301-796-2302
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Bugin, Kevin

m:	Bugin, Kevin
t:	Monday, July 11, 2011 3:47 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Clinical Pharmacology Follow Up Information Request - July 11, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the clinical pharmacology data and your recent response to information request, we have the following comments:

1. In your response to the Agency's May 23 Clinical Pharmacology Information Request, dated June 6, 2011, you did not explain why the serum sample should be collected within 30 days after an adalimumab dose. Please provide the rationale for this criterion.

2. You reported that, in Study 827, the immunogenicity rate was 3.9% (19/487). We do not agree with the denominator you used in the calculation as it led to an underestimation of the true immunogenicity rate. We understand that the denominator of 487 reflects the number of enrolled subjects who had eligible data for PK analyses; i.e., the total number of subjects enrolled **(n=518) in the study minus the number of subjects who did not** have eligible PK samples (n=31). However, this denominator inappropriately included the patients who had adalimumab concentrations greater than 2 µg/mL in all post-dose samples during the study and were not tested for anti-adalimumab antibodies. In addition, the denominator may have included the patients who did not have appropriate samples for immunogenicity testing such as in the following scenarios:
    i. no immunogenicity samples were taken;
    ii. the only immunogenicity sample taken was at baseline; or
    iii. immunogenicity samples had insufficient volume for analysis.

    Please recalculate the rate of antibody development.

    When you submit the recalculation, please also submit the SAS transport file with coding reflecting cases mentioned above.

If you have any questions, please do not hesitate to contact me.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
ER/Office of Drug Evaluation III
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

Reference ID: 3200370

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Please consider the environment before you print.

Bugin, Kevin

om:	Bugin, Kevin
ent:	Monday, May 23, 2011 1:20 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Clinical Pharmacology Information Request - May 23, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the pharmacology sections of your supplement, we have the following comments:

In your summary of clinical pharmacology studies (page 20, Module 2.7.2), you stated that "A sample was classified as AAA positive if the AAA concentration in serum was > 20 ng/mL, the signal was reduced by < 50% by addition of 10% normal human serum, and the serum sample was collected within 30 days after an adalimumab dose for Studies M02-403, M04-691 and M02-433. For Study M06-827, the AAA positive criteria were defined as the AAA concentration in serum was > 20ng/mL and the serum sample was collected within 30 days after an adalimumab dose."

Please clarify your rationale for each of the criteria and explain why different criteria were used for different studies.

Kind regards,
Kevin

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
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Please consider the environment before you print.

Bugin, Kevin

rom:	Bugin, Kevin
ent:	Monday, May 09, 2011 1:52 PM
To:	'Bonnie W Kain'
Cc:	Bugin, Kevin
Subject:	BLA 125057/232 - Statistics Information Request - May 09, 2011
Follow Up Flag:	Follow up
Flag Status:	Flagged

Our STN: BL 125057/232

Hi Bonnie,

Please refer to the supplement to your biologics license application (BLA) received January 25, 2011, submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

During the review of the statistical and clinical sections of your supplement, we have the following comment:

ease perform additional sensitivity analyses for the primary clinical endpoint for Study M06-826, co-primary endpoints and e 1st ranked secondary endpoint for Study M06-827. These additional sensitivity analyses will include CC (complete case), **C (observed case) and multiple imputation.**

you have any questions, please do not hesitate to contact me.

ards,

Kevin Bugin, MS, RAC
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/Office of Drug Evaluation III
US Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-002
P-301-796-2302

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125057/232

FILING ISSUES
April 08, 2011

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to the supplement to your biologics license application (BLA), dated Janurary 25, 2011, and submitted under section 351 of the Public Health Service Act, for Humira (adalimumab). Also refer to our filing letter dated March 25, 2011.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The SPL version of the labeling included in the January 25, 2011 submission did not include the required Highlights section. Please review and correct if necessary the formatting/coding of the SPL.
2. A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year. Ensure that labeling is updated accordingly, during the course of the review.
3. The revision date will be the month/year of supplement approval. Use a placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," at the end of the Highlights section.
4. The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1). Note, the subsection currently named [redacted] (b) (4) should be changed to "Clinical Trials Experience". Also note, the heading titled Other Adverse Reactions in Section 6 Adverse Reactions is duplicated
5. Under the Adverse Reactions section, for the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

   > The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to [redacted] (b) (4) exposure.

We request that you resubmit labeling that addresses these issues by April 29, 2011 The resubmitted labeling will be used for further labeling discussions.

Please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

/Richard W. Ishihara/
Richard W. Ishihara
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

MEMO OF FILING MEETING

DATE: 03/08/2011

BLA/NDA/Supp #: 125057/232

PROPRIETARY NAME: Humira

ESTABLISHED/PROPER NAME: Adalimumab

DOSAGE FORM/STRENGTH: Injection 40 mg/0.8 mL and 20 mg/0.4 mL

APPLICANT: Abbott Laboratories, Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

BACKGROUND: In December 2002, adalimumab was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) in the United States (US). On 27 February 2007, adalimumab was approved in the US for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Adalimumab has also been approved for indications in psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kevin Bugin	Y
	CPMS/TL:	Richard W Ishihara	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Clinical	Reviewer:	Aisha Peterson	Y
	TL:	Rob Fiorentino	Y
Social Scientist Review (*for OTC products*)	Reviewer:		

Reference ID: 3200370

	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Reference ID: 3200370

Clinical Pharmacology	Reviewer:	Lucy Fang	Y
	TL:	Yowming Wang	Y
Biostatistics	Reviewer:	Milton Fan	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sushanta Chakder	Y
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	Jun Park	N
	TL:		
Product Quality (CMC)	Reviewer:	Jun Park	N
	TL:		
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Nitin Patel	Y
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Reference ID: 3200370

Bioresearch Monitoring (DSI)	Reviewer:	Khairy Malek	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no,** explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments:** N/A	☐ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

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or efficacy issues ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments:** Submitted assay was per a previous supplement review and information request. Reviewer will prepar a memo to the effect that it is not needed for review in this supplement.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:** See above comment. No other CMC aspects.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no,** was a complete EA submitted? **If EA submitted,** consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)** **Comments:**	☐ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:** will be submitted following 74 day letter.	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

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Facility/Microbiology Review (BLAs only) **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments:**	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Donna Griebel, M.D.

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

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☒	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

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Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 125057/232

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGEMENT
February 10, 2011

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to your Supplemental Biologics License Application (sBLA) dated January 25, 2011, received January 25, 2011, submitted under section 351 of the Public Health Service Act for the following:

BL NUMBER:	125057/232
PRODUCT NAME:	Humira (adalimumab)
DATE OF SUBMISSION:	JANUARY 25, 2011
DATE OF RECEIPT:	JANUARY 25, 2011

This supplemental application proposes the following change: reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 26, 2011 in accordance with 21 CFR 601.2(a). If the application is filed, the user fee goal date will be November 25, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-2302.

Sincerely,

/ Kevin Bugin /
Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 125057/232

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

This letter is in regard to the supplement to your biologics license application (BLA), received January 25, 2011, and submitted under section 351 of the Public Health Service Act, for Humira (adalimumab).

We have completed an initial review of your supplement to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your supplement today. The review classification for this supplement is Standard. Therefore, the user fee goal date is November 25, 2011. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before April 10, 2011.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kevin Bugin, Regulatory Project Manager, at (301) 796-2302.

Sincerely,

/Donna Griebel/
Donna Griebel, M.D.
Director
Division of Division Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100103

MEETING MINUTES

Abbott Laboratories
Attention: Bonnie Kain
Associate Director
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Kain:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Humira (adalimumab).

We also refer to the meeting between representatives of your firm and the FDA on November 23, 2010. The purpose of the meeting was to discuss the submission of a supplemental Biologics License Application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2302.

Sincerely,

{See appended electronic signature page}

Kevin Bugin, M.S., R.A.C.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sBLA
Meeting Date and Time:	**November 23, 2010, 3:00 – 4:00 p.m. EST**
Meeting Location:	10903 New Hampshire Avenue, White Oak Building 22, Conference Room 1315, Silver Spring, Maryland 20903
Application Number:	IND 100103
Product Name:	Humira (adalimumab)
Indication:	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
Sponsor/Applicant Name:	Abbott Laboratories
Meeting Chair:	Robert Fiorentino
Meeting Recorder:	Kevin Bugin

FDA ATTENDEES

Division of Gastroenterology Products
Donna Griebel, M.D., Director, (attended via phone)
Robert Fiorentino, M.D., M.P.H., Medical Team Leader
Ii-Lun Chen, M.D., Medical Reviewer
Fang Cai, Ph.D., Pharmacology Reviewer
Kevin Bugin, M.S., R.A.C., Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology III
Jang-Ik Lee, Pharm.D., Ph.D., Biopharmaceutics Reviewer

Office of Clinical Pharmacology
Christine Garnett, Pharm.D., Pharmacometrics Team Leader

Office of Biostatistics, Division of Biometrics III
Milton Fan, Ph.D., Biometrics Reviewer

Office of Biotechnology Products, Division of Monoclonal Antibodies
Jun Park, Ph.D., Reviewer

Reference ID: 3200370

SPONSOR ATTENDEES
Abbott Laboratories
Lauren Hetrick, Senior Director, Regulatory Policy and Intelligence

Bidan Huang, PhD, Associate Director, Global Statistics and Data Management

Bonnie Kain, Associate Director, Global Pharmaceutical Regulatory Affairs

Andreas Lazar, MD, Associate Medical Director, Global Pharmaceutical Research and Development

John Medich, Divisional Vice President, Clinical Development

Susan Paulson, PhD , Director, Clinical Pharmacokinetics and Pharmacometrics

Mary Beth Tighe, PhD , Associate Director, Clinical Program Management

Raymond Votzmeyer, MBA , Director , Global Pharmaceutical Regulatory Affairs

Roopal Thakkar, MD, Project Director, Global Pharmaceutical Research and Development (attended via phone)

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1.0 BACKGROUND

In December 2002, Humira (adalimumab) was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis in the US. In February 2007, Humira was approved for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to **severely active Crohn's disease** (CD) who have had an inadequate response to conventional therapy, and reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. Humira has also been approved for psoriatic arthritis, Ankylosing Spondylitis, juvenile idiopathic arthritis and plaque psoriasis.

On September 15, 2010, Abbott Laboratories submitted a meeting request and briefing package to discuss the submission of a supplemental Biologics License Application for use of Humira in reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The meeting **was granted on September 28, 2010. The FDA's** preliminary comments to the questions in the briefing package were communicated to Abbott Laboratories on November 18, 2010. The meeting between Abbott Laboratories and the DGP was held as scheduled on November 23, 2010.

2. DISCUSSION

(Questions in the briefing package **are shown in plain font. FDA**'s preliminary responses are shown in **boldface**. Discussion at the meeting is shown in ***bold italics***.)

Clinical

1. Abbott believes that the scope of the clinical program is sufficient to support the planned sBLA for the proposed indication of reducing signs and symptoms, and inducing and maintaining induction of clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

   Study M06-826 met the primary endpoint of clinical remission at Week 8 (P = 0.031), and Study M06-827 met the co-primary endpoints of clinical remission at Week 8 (P = 0.019) and clinical remission at Week 52 (P = 0.004), as well as the first ranked secondary endpoint of clinical remission at both Weeks 8 and 52 (P = 0.047). Durability of sustained clinical remission is demonstrated by the result of the first ranked secondary endpoint of remission at both Week 8 and Week 52, as well as a statistically significantly greater proportion of subjects in sustained clinical remission and sustained clinical response at Weeks 8, 32, and 52 for the adalimumab 160/80/40 group compared to the placebo group. Sustained effectiveness of adalimumab in the maintenance of clinical remission in subjects who had previously achieved clinical remission after adalimumab induction therapy is supported by the results from the open-label maintenance period of Study M06-826 and interim results from open-label extension Study M10-223.

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We believe that the trial designs and statistical methodology are adequate to demonstrate safety and efficacy of adalimumab for the treatment of UC. Does the Agency agree?

FDA Response:

The trial designs, in general, appear appropriate for evaluating the efficacy and safety of Humira for the treatment of UC. However, the adequacy of the trial results to support the proposed indication will be a review issue. Furthermore, the specific wording of the indication statement will be a review issue based on the evaluation of the BLA submission.

Assuming that your Statistical Analysis Plan (SAP) followed previous FDA recommendations, the methodology should be appropriate for analyzing the data.

Please note that the Division's current recommendations are that "clinical response" be defined as a decrease in Mayo score from Baseline ≥ 3 *AND* a 30% decrease in Mayo score, along with either a decrease in rectal bleeding score ≥ 1 *OR* absolute rectal bleeding score ≤ 1. An endpoint of "clinical remission" should include a rectal bleeding score of 0 and no friability on endoscopy. Please incorporate this definition of clinical remission into a post-hoc sensitivity analysis.

Abbott Response:

Abbott understands the Division's current recommendation regarding "clinical response." In the protocol our pre-specified definition for clinical response is the same as defined by **the Division's current recommendation:**

- A decrease in Mayo score from Baseline ≥ 3, and,
- A 30% decrease in Mayo score,
- Along with either a decrease in rectal bleeding score ≥ 1 or *absolute* rectal bleeding score ≤ 1.

Abbott Response: Protocol Definition of Clinical Remission as Applied (Mayo score ≤2 with no subscore >1)

Parameter	Score			
	0	1	2	3
Stool frequency	Normal for patient	1–2 more than normal	3–4 more than normal	≥5 more than normal
Rectal bleeding	None	Streaks less than 50% of time	Obvious blood most of the time	Blood alone passed
Endoscopy findings	Normal/ inactive	Mild disease (e.g. mild friability)	Moderate disease (e.g. friability)	Severe disease
Physician's global assessment	Normal	Mild	Moderate	Severe

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We would like to seek clarity regarding the Division's definition to be used regarding the current recommendation for the post hoc analysis of "clinical remission."

Discussion:
The Division will follow up with a specific recommendation for the definition of clinical remission.

Post-Discussion FDA Comments: ***The Division recommends that the post hoc analysis utilize a definition of Clinical Remission as total Mayo score ≤2 with rectal bleeding subscore=0 (no bleeding) and endoscopy subscore=0 (e.g., no friability). If collected, Mayo subscores for each subject should be provided in the datasets.***

2. Abbott believes that the number of subjects on adalimumab treatment in the clinical program (N = 995) and the length of time for subject follow-up to be included in the planned sBLA (1041 patient-years of adalimumab exposure based on a 31 December 2009 data cut-off for the MI 0-223 interim clinical study report) will provide adequate characterization of the safety of adalimumab in UC, particularly in view of the large safety database in rheumatoid arthritis as well as CD patients treated with adalimumab. Does the Agency agree?

FDA Response:
On its face, the patient safety database appears to be adequate; however, the adequacy of the safety database to support the indication is a review issue.

Discussion:
No further discussion.

3. Abbott proposes that the 120-day safety update will contain safety data from subjects in Study M10-223 with cumulative exposure to adalimumab from 01 January 2010 through 01 December 2010. Does the Agency agree with the proposed period for the 120-day safety update?

FDA Response:
Please provide an overview of the extent to which these dates will capture cumulative exposure data. If the submission of the BLA is significantly delayed, additional safety data beyond December 2010 may need to be provided. Within the 120-day safety update, please also include any additional safety data from Study M06-826 and M06-827 collected during this time period.

Discussion:
No further discussion.

4. Abbott plans to propose an induction dose of 160 mg at Week 0 and 80 mg at Week 2. The proposed induction dose is supported by the statistically significant results from Study M06-S26 and Study M06-S27. Does the Agency agree with the proposed induction dose?

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FDA Response:
The proposed induction dose is a review issue.

Discussion:
No further discussion.

5. The initial induction dose of 160 mg requires four injections in a single day. This regimen may be inconvenient for some patients. Abbott intends to provide data from pharmacokinetic modeling and simulation to support the administration of the 160 mg dose over an interval of 2 days. Pharmacokinetic modeling and simulation was used to support the above approved induction dosing over a 2-day interval for approval of the indication for CD. Would the Agency consider the plan for pharmacokinetic modeling and simulation, as described in Section 13.0 of this document, to be adequate to support this alternative induction dosing regimen for product labeling for UC?

FDA Response:
The approach proposed to support this alternative induction dosing regimen is acceptable.

Discussion:
No further discussion.

Regulatory

6. Abbott proposes the integration of the efficacy and safety data from Studies M06-826, M06-827 and M10-223 as described in the attached ISE and ISS SAPs (Appendix D and Appendix E, respectively). Does the Agency agree? Does the Agency have any comments on the proposed ISE and ISS SAPs?

FDA Response:
Regarding the ISS, please provide analyses of placebo compared to both the 80/40 and 160/80 treatment arms in order to establish whether there is a dose response safety signal.

For the ALL ADA set, in addition to your proposed analysis, please also provide a comparison of those on treatment in trials M06-826 and M06-827 compared to placebo from M06-827.

Abbott Response:

We would like to provide clarification regarding the analysis in the ISS.

Given that study M06-826 has no placebo beyond week 8 due to crossover to adalimumab treatment, an analysis of placebo compared to both the 80/40 and 160/80

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treatment arms will be conducted for the 8-week, double-blind induction period. This will be an integrated analysis of M06-826 and M06-827.

The ALL ADA Set includes any subject who received at least one dose of adalimumab, including placebo patients that crossover.

We will provide a comparison of adverse events for the ALL ADA exposure to the placebo exposure in M06-826 and M06-827, using exposure-adjusted analysis (event per 100 patient-years).

Discussion:
Abbott will provide the analysis as requested: a single table comparing the two single doses for the double-blind 8-week induction period to placebo.

The Agency agrees with the initial approach proposed for the ALL ADA Set suggested by Abbott and clarified in their response.

7. Abbott proposes that the analysis ready data sets and analysis ready programs for data from the three studies (Studies M06-826, M06-827, and M10-223) be provided only for the ISE and ISS, and case report tabulation data sets be provided for individual studies. Abbott believes that the planned structure and content of these documents, included as Appendix F, should provide reviewers with complete analyses of key safety parameters, and a thorough evaluation of any identified safety issues, as well as the primary efficacy and key secondary endpoints as defined in the study protocols. Does the Agency agree with the proposal?

FDA Response:
The Agency does not agree with the proposed plan to submit analysis ready data sets and programs for only the ISE and ISS. For each adequate and well-controlled clinical study in your BLA you should provide the following:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Transport, along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf). We

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recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.

3. A well commented and organized program (e.g. utilizing SAS) written for each analysis dataset and efficacy table created.

Abbott Response:
We are meeting the request as specified in Item #1, by including Case Report Form Tabulation electronic datasets with thorough data define files and annotated case report forms. Although the submission will not be CDISC/SDTM compliant, the datasets will be consistent across studies to allow pooling of data (with reference to the Agency response to Question 9).

Regarding Item #2, the ISS and ISE will include all corresponding analysis ready datasets, submitted utilizing SAS Transport, along with a thorough data definition file. Abbott proposes to include the analysis ready data sets for the 3 individual studies (M06-826, M06-827, M10-223) within **60 days** of submitting the supplemental application (sBLA).

Does the Agency agree to this proposal?

Regarding Item #3, for all the analyses proposed in Appendix F of the Meeting Information Package (Proposal for Analysis Ready Data Sets and Programs), we will submit well commented and organized programs.

Discussion:
Abbott and the Agency are in agreement with Abbott response to items 1 and 3, above. For item 2, above, the Agency requests to have the analysis ready datasets for the two individual studies (M06-826 and M06-827) at the time of submission of the sBLA.

8. Abbott will be requesting a waiver for the evaluation of adalimumab use in pediatric UC patients given the low prevalence of disease in pediatric patients less than 6 years of age and a deferral for patients (b) (4) 17 years of age (inclusive). Abbott intends to seek Agency advice on the design of the pediatric development program via a separate Type-B meeting request. Does the Agency agree with Abbott's plans to address pediatric DC?

FDA Response:
Please submit a pediatric plan at the time of your BLA submission. Include in the plan the studies ongoing and planned, the specific age groups that will be studied, and any age groups to be deferred or waived along with the associated timelines. All age groups (ages 0 months through 17 years) must be addressed in the pediatric plan and certification of the grounds for deferring any assessments should be included. The proposed pediatric plan should be appropriately supported by epidemiological data. Furthermore, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time should be provided in the plan.

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For information on acceptable criteria for deferrals see Section 505B(a)(3) of the Federal Food, Drug, and Cosmetic Act and how to apply for a deferral, please refer to the draft guidance document, *Guidance for Industry – How to Comply with the Pediatric Research Equity Act*, which is available at:

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf

Abbott Response:
We would like to confirm that we will include the pediatric plan for Ulcerative Colitis in the sBLA submission. We also plan to request a Type B meeting with the Agency to discuss the pediatric plan, including the pediatric study design, and information about the EU PIP, in 2011.

Discussion:
Abbott and the Agency are in agreement. Abbott will submit a pediatric plan at the time of the sBLA submission, and intends to request a Type B meeting to discuss the specific details of the pediatric plan (i.e. Trial Design).

9. For the planned sBLA, Abbott plans to provide electronic Common Technical Document (eCTD)-formatted documents mapped to an eBLA structure. The planned sBLA will conform to the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008). Does the Agency agree that the proposed format and content for the planned sBLA, as presented in Section 14.0, is adequate and appropriate?

FDA Response:
Submission in electronic Common Technical Document format is appropriate and preferred. For questions on the adequacy of your submission or the submission we recommend contacting esub@fda.hhs.gov. Regarding data, CDISC format is strongly preferable. Please refer to response to Question 7, above. If you are using a different format, the datasets should at least be consistent across studies so that data may be pooled.

Discussion:
No further discussion.

We have the following additional requests:

1. **Include a detailed regulatory history of the clinical development of your drug. Please also provide a description of each major amendment made to the protocols.**

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Discussion:
No further discussion.

2. **It is not clear what CRFs will be submitted with the sBLA or which will be available upon request. Please plan to provide electronic case report forms for all patients reporting a serious adverse event. We also seek assurance that CRFs for subjects who discontinued study treatment or study participation will be available. Please clarify.**

Abbott Response:
CRFs to be included in the submission will be for deaths, SAEs, and adverse events leading to discontinuations.

CRFs for subjects who discontinued study treatment or study participation will be available upon request.

Discussion:
The Agency agrees with the proposal.

3. **Please clarify whether or not all adverse events, as opposed to only treatment emergent adverse events, will be available in the study datasets.**

4. **Please ensure that investigator verbatim AE terms will also be included in the datasets.**

Abbott Response:
We will be providing Case Report Form Tabulations (CRTs) electronic datasets that include all adverse events, including the investigator verbatim AE terms.

However, the Analysis Ready Datasets will include treatment emergent adverse events and will include System Organ Class (SOC) and preferred terms. Does the Agency agree with this approach?

Discussion:
The Agency agrees with the proposal.

5. **For your population PK/PD analyses, all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a data definition file (Define.xml or Define.pdf). Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the**

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population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion:
No further discussion.

6. **Include a thorough review of data relevant to the safety of your product that includes a literature review regarding the safety of your drug and the safety of other similar products currently on the market.**

Abbott Response:
We propose that this review is specific to adalimumab for ulcerative colitis and the other anti-TNF approved for this indication. Does the Agency agree? Are there other specific aspects that the Agency would like to see included in this review?

Discussion:
The Agency requests a thorough literature review of the Safety of TNF blockers as a drug class and not just the use of TNF blockers in the UC indication. Abbott agreed to the Agency's request.

7. **Please provide updated information on the immunogenicity assay(s) used to evaluate anti-adalimumab antibody (AAA). Confirm that the validated immunogenicity assay(s) approved under the BLA are in use and that the sensitivity of the AAA assay to product interference at the level of product expected to be present at the time AAA samples are taken is adequate. Provide information on the relative level of AAA that would be detected by the assay at this product concentration.**

Discussion:
No further discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

Slides presented by Abbott Laboratories are attached.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEVIN B BUGIN
11/30/2010