CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125057Orig1s356

Trade Name:	HUMIRA
Generic or Proper Name:	Adalimumab injection
Sponsor:	AbbVie, Inc.
Approval Date:	September 23, 2014
Indication:	This prior approval supplemental biologics application provides for the use of HUMIRA (adalimumab) for the treatment of pediatric Crohn's Disease: Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125057/ 356

SUPPLEMENT APPROVAL

AbbVie Inc
Attention: Denise Farmer
Manager, Regulatory Affairs, US & Canada
1 N. Waukegan Rd; AP30-1 Dept. PA77
North Chicago, IL 60064-3537

Dear Ms. Farmer:

Please refer to your Supplemental Biologics License Application (sBLA), dated August 29, 2013, received August 29, 2013, submitted under section 351(a) of the Public Health Service Act for Humira (adalimumab).

We acknowledge receipt of your amendments dated September 26, 2013, October 3, 2013, October 10, 2013, November 18, 2013, December 27, 2013, January 14, 2014, January 21, 2014, January 30, 2014, February 28, 2014, March 17, 2014, April 14, 2014, May 19, 2014, June 4, 2014, June 13, 2014, July 30, 2014, August 6, 2014, August 21, 2014, September 3, 2014, September 5, 2014, September 12, 2014, September 16, 2014, September 19, 2014, and September 22, 2014.

This Prior Approval supplemental biologics application proposes expanding the patient population to include pediatric Crohn's disease patients aged 6 years or older and the introduction of a 10 mg/0.2 mL pre-filled syringe.

APPROVAL & LABELING

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.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes 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 September 12, 2014, 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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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 CDR Matthew Brancazio, Pharm.D., Regulatory Project Manager, at (301) 796-5343.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
Content of Labeling
Carton and Container 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
09/23/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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, Pediatric Crohn's Disease (1.6)	9/2014
Dosage and Administration, Pediatric Crohn's Disease (2.4)	9/2014
Dosage and Administration, General Considerations for Administration (2.8)	9/2014

----------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.
- **Adult 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.
- **Pediatric Crohn's Disease (1.6):** Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.
- **Ulcerative Colitis (UC) (1.7):** 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) (1.8):** 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

Adult Crohn's Disease and Ulcerative Colitis (2.3, 2.5):
- 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.

Pediatric Crohn's Disease (2.4)
- ***17 kg (37 lbs) to < 40 kg (88 lbs):***
  - Initial dose (Day 1): 80 mg (two 40 mg injections in one day)
  - Second dose two weeks later (Day 15): 40 mg
    - Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week.
- ***≥ 40 kg (88 lbs):***
  - 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 40 mg injections in one day)
    - Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.

Plaque Psoriasis (2.6):
- 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)
- Injection: 10 mg/0.2 mL in a single-use prefilled glass syringe (3)
- Injection: 40 mg/0.8 mL in a single-use glass vial for institutional use only (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 AbbVie Inc. 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.

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 have 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 Adult 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 Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

1.7 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 (14.7)]*.

1.8 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 Adult 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 Pediatric Crohn's Disease

The recommended HUMIRA dose regimen for pediatric patients 6 years of age and older with Crohn's disease (CD) is based on body weight as shown below:

Pediatric Patients	Induction Dose	Maintenance Dose Starting at Week 4 (Day 29)
17 kg (37 lbs) to < 40 kg (88 lbs)	• 80 mg on Day 1 (administered as two 40 mg injections in one day); and • 40 mg two weeks later (on Day 15)	• 20 mg every other week
≥ 40 kg (88 lbs)	• 160 mg on Day 1 (administered as four injections in one day or as two 40 mg injections per day for two consecutive days); and • 80 mg two weeks later (on Day 15) (administered as two 40 mg injections in one day)	• 40 mg every other week

2.5 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.

2.6 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.

2.7 Monitoring to Assess Safety

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

2.8 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, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

The HUMIRA institutional use vial is for use and administration within an institutional setting only, such as a hospital, physician's office or clinic. Withdraw the dose using a sterile needle and syringe and administer promptly by a healthcare provider within an institutional setting. Only administer one dose per vial. The vial does not contain preservatives; therefore, discard unused portions.

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.

Injection: A single-use, 1 mL prefilled glass syringe with a fixed 27 gauge ½ inch needle, providing 10 mg/0.2 mL of HUMIRA.

- **Institutional Use Vial**

Injection: A single-use, glass vial, providing 40 mg/0.8 mL of HUMIRA for institutional use only.

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 and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) 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. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. 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 have 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. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

5.3 Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported 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 (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

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 pediatric 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 a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); 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 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 adult patients with CD with a 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 the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. 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 adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

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 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/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 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/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.

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.

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

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 regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, and Ps. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

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

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant blood, and 0-16.1 µg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data

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.

8.3 Nursing Mothers

Limited data from published literature indicate that adalimumab is present in low levels in human milk and is not likely to be absorbed by a breastfed infant. However, no data is available

on the absorption of adalimumab from breastmilk in newborn or preterm infants. Caution should be exercised when HUMIRA is administered to a nursing woman.

8.4 Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations (8.1)]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

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

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)]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies (14.6)]*.

The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

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 patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients 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 40 mg/0.8 mL prefilled syringe, prefilled pen or single-use institutional use vial delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains adalimumab 40 mg, citric acid monohydrate 1.04 mg, dibasic sodium phosphate dihydrate 1.22 mg, mannitol 9.6 mg, monobasic sodium phosphate dihydrate 0.69 mg, polysorbate 80 0.8 mg, sodium chloride 4.93 mg, sodium citrate 0.24 mg and Water for Injection, USP. Sodium hydroxide is added as necessary to adjust pH.

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

Each 10 mg/0.2 mL prefilled syringe delivers 0.2 mL (10 mg) of drug product. Each 0.2 mL of HUMIRA contains adalimumab 10 mg, citric acid monohydrate 0.26 mg, dibasic sodium phosphate dihydrate 0.31 mg, mannitol 2.4 mg, monobasic sodium phosphate dihydrate 0.17 mg, polysorbate 80 0.2 mg, sodium chloride 1.23 mg, sodium citrate 0.06 mg and Water for Injection, USP. Sodium hydroxide is 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.

In pediatric subjects with CD weighing ≥ 40 kg, the mean ±SD serum adalimumab concentrations were 15.7±6.5 mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 10.5±6.0 mcg/mL at Week 52 following subcutaneous doses of 40 mg every other week. In pediatric subjects with CD weighing < 40 kg, the mean ±SD serum adalimumab concentrations were 10.6±6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab

concentrations were 6.9±3.6 mcg/mL at Week 52 following subcutaneous doses of 20 mg every other week.

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

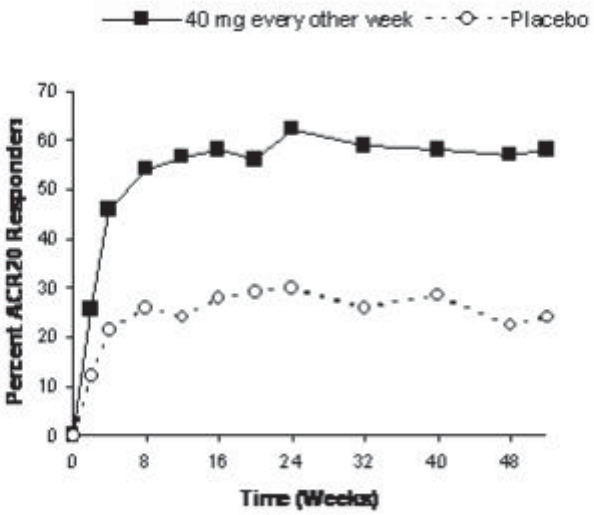
	Study RA-II				Study RA-III			
Parameter (median)	**Placebo N=110**		**HUMIRA[a] N=113**		**Placebo/MTX N=200**		**HUMIRA[a]/MTX N=207**	
	Baseline	**Wk 26**	**Baseline**	**Wk 26**	**Baseline**	**Wk 24**	**Baseline**	**Wk 24**
Number of tender joints (0-68)	35	26	31	16*	26	15	24	8*
Number of swollen 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.

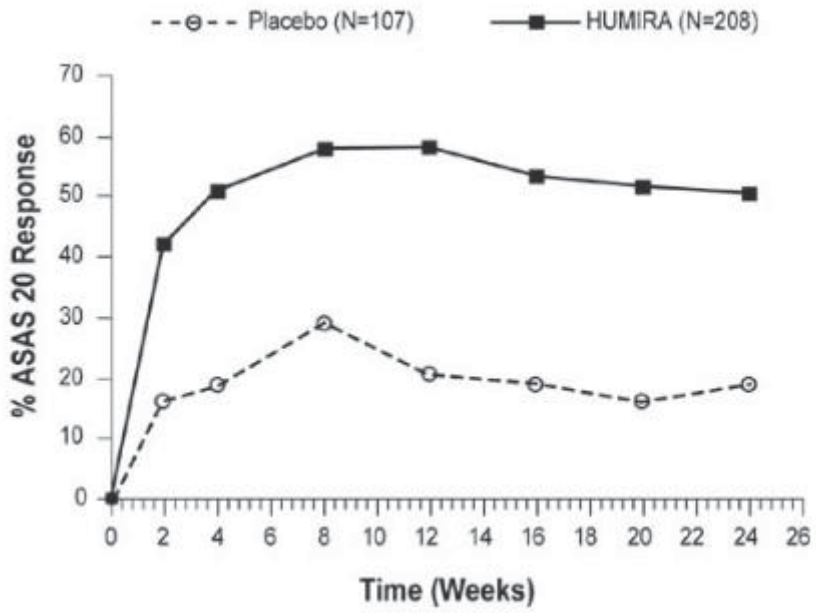
14.4 Ankylosing Spondylitis

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 Adult 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 Pediatric Crohn's Disease

A randomized, double-blind, 52-week clinical study of 2 dose levels of HUMIRA (Study PCD-I) was conducted in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease (defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30).[2] Enrolled patients had over the previous two year period an inadequate response to corticosteroids or an immunomodulator (i.e., azathioprine, 6-mercaptopurine, or methotrexate). Patients who had previously received a TNF blocker were allowed to enroll if they had previously had loss of response or intolerance to that TNF blocker.

Patients received open-label induction therapy at a dose based on their body weight (≥40 kg and <40 kg). Patients weighing ≥40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing <40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥40 kg and <40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥40 kg and 20 mg every other week for patients weighing <40 kg. The low dose was 20 mg every other week for patients weighing ≥40 kg and 10 mg every other week for patients weighing <40 kg.

Concomitant stable dosages of corticosteroids (prednisone dosage ≤40 mg/day or equivalent) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted throughout the study.

At Week 12, patients who experienced a disease flare (increase in PCDAI of ≥ 15 from Week 4 and absolute PCDAI > 30) or who were non-responders (did not achieve a decrease in the PCDAI of ≥ 15 from baseline for 2 consecutive visits at least 2 weeks apart) were allowed to dose-escalate (i.e., switch from blinded every other week dosing to blinded every week dosing); patients who dose-escalated were considered treatment failures.

At baseline, 38% of patients were receiving corticosteroids, and 62% of patients were receiving an immunomodulator. Forty-four percent (44%) of patients had previously lost response or were intolerant to a TNF blocker. The median baseline PCDAI score was 40.

Of the 192 patients total, 188 patients completed the 4 week induction period, 152 patients completed 26 weeks of treatment, and 124 patients completed 52 weeks of treatment. Fifty-one percent (51%) (48/95) of patients in the low maintenance dose group dose-escalated, and 38% (35/93) of patients in the high maintenance dose group dose-escalated.

At Week 4, 28% (52/188) of patients were in clinical remission (defined as PCDAI ≤ 10).

The proportions of patients in clinical remission (defined as PCDAI ≤ 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52.

At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group (Table 13). The recommended maintenance regimen is 20 mg every other week for patients weighing < 40 kg and 40 mg every other week for patients weighing ≥ 40 kg. Every week dosing is not the recommended maintenance dosing regimen *[see Dosage and Administration (2.4)]*.

Table 13. Clinical Remission and Clinical Response in Study PCD-I

	Low Maintenance Dose[†] (20 or 10 mg every other week) N = 95	**High Maintenance Dose[#] (40 or 20 mg every other week) N = 93**
Week 26		
Clinical Remission[‡]	28%	39%
Clinical Response[§]	48%	59%
Week 52		
Clinical Remission[‡]	23%	33%
Clinical Response[§]	28%	42%

[†]The low maintenance dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing < 40 kg.
[#]The high maintenance dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg.
[‡]Clinical remission defined as PCDAI ≤ 10.
[§]Clinical response defined as reduction in PCDAI of at least 15 points from baseline.

14.7 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 14).

Table 14. 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.

14.8 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 15 and 16).

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 15. 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 16. 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.
2. Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12:439-447.

16 HOW SUPPLIED/STORAGE AND HANDLING

HUMIRA® (adalimumab) is supplied 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 Prefilled Syringe - Pediatric Crohn's Disease Starter Package (6 count)**

HUMIRA is dispensed in a carton containing 6 alcohol preps and 6 dose trays (Pediatric Starter Package). 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 0074-3799-06.

- **HUMIRA Prefilled Syringe - Pediatric Crohn's Disease Starter Package (3 count)**

HUMIRA is dispensed in a carton containing 4 alcohol preps and 3 dose trays (Pediatric Starter Package). 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 0074-3799-03.

- **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.

- **Prefilled Syringe Carton - 20 mg**

HUMIRA is supplied 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.

- **Prefilled Syringe Carton - 10 mg**

HUMIRA is supplied 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 10 mg/0.2 mL of HUMIRA. The NDC number is 0074-6347-02.

- **Institutional Use Vial Carton - 40 mg**

HUMIRA is supplied for institutional use only in a carton containing a single-use, glass vial, providing 40 mg/0.8 mL of HUMIRA. The NDC number is 0074-3797-01.

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.

AbbVie Inc.

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

US License Number 1889

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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
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- 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.
    - **moderate to severe Crohn's disease (CD) in children** 6 years and older 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 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.
- 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 over-the-counter 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 health 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: citric acid monohydrate, dibasic sodium phosphate dihydrate, mannitol, monobasic sodium phosphate dihydrate, polysorbate 80, sodium chloride, sodium citrate 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.

Manufactured by:

AbbVie Inc.

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

US License Number 1889

Revised: 9/2014

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 and have read and understand this Instructions for Use. 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. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. 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?

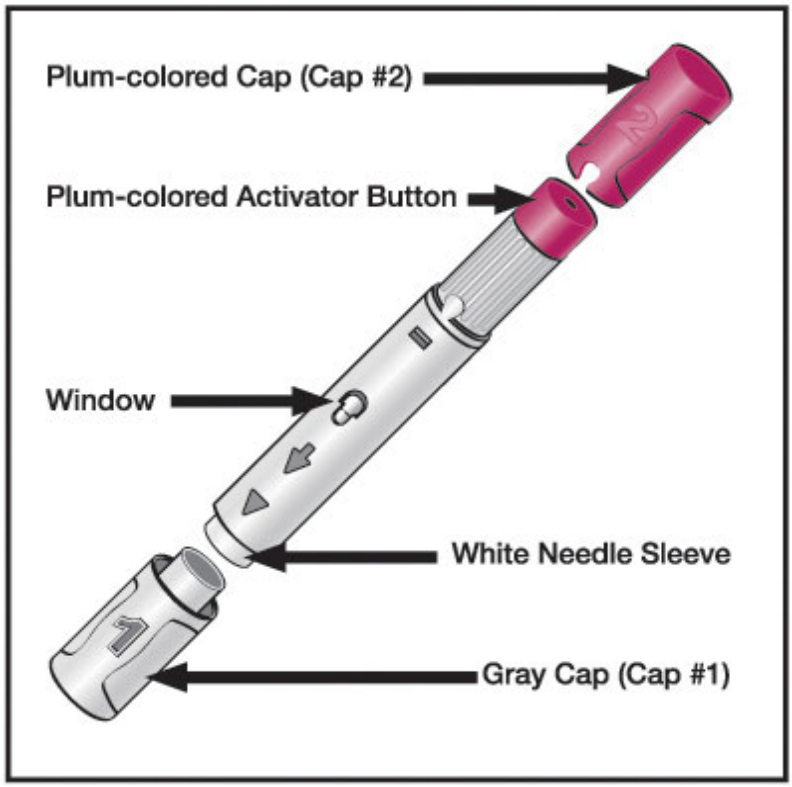
- Store HUMIRA in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
- When traveling, HUMIRA should be stored in a cool carrier with an ice pack.
- **Do not freeze HUMIRA.** Do not use HUMIRA if frozen, even if it has been thawed.
- Refrigerated 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 each 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)
  - 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:

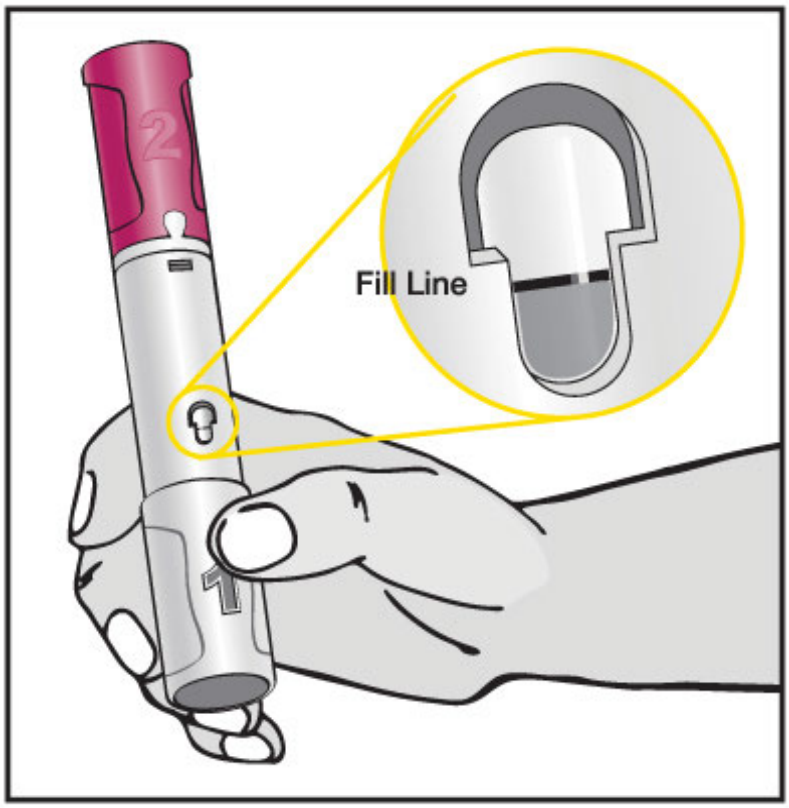
- you drop or crush your HUMIRA Pen.
- the seals on the top or bottom of the carton are broken or missing.
- the expiration date on the carton, dose tray, and Pen has passed.
- the HUMIRA Pen has been frozen or left in direct sunlight. See the section: **"How should I store HUMIRA?"** at the beginning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

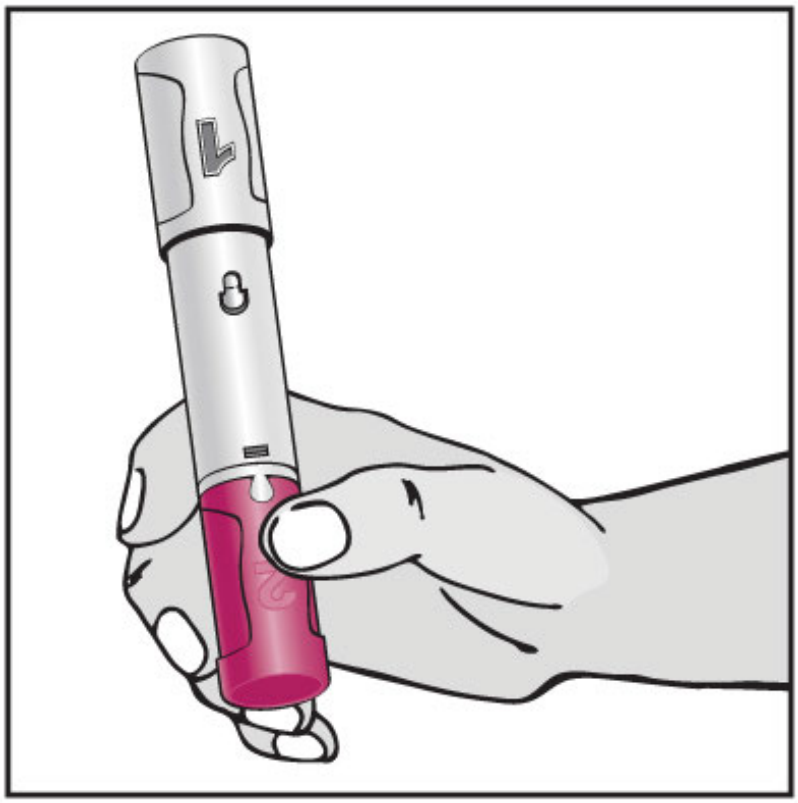
Figure B



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



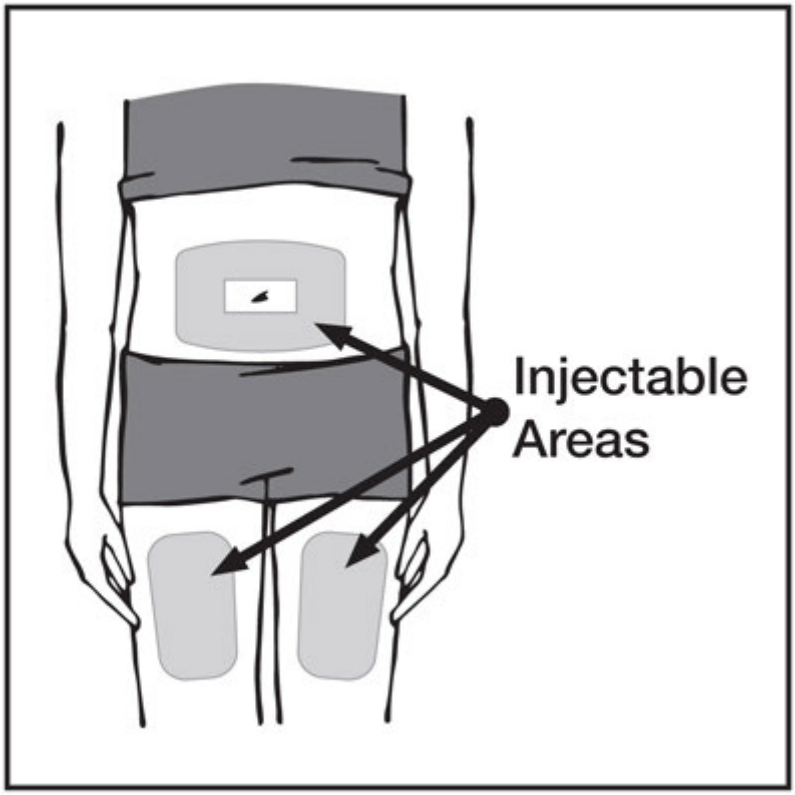
Choose the Injection Site

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.

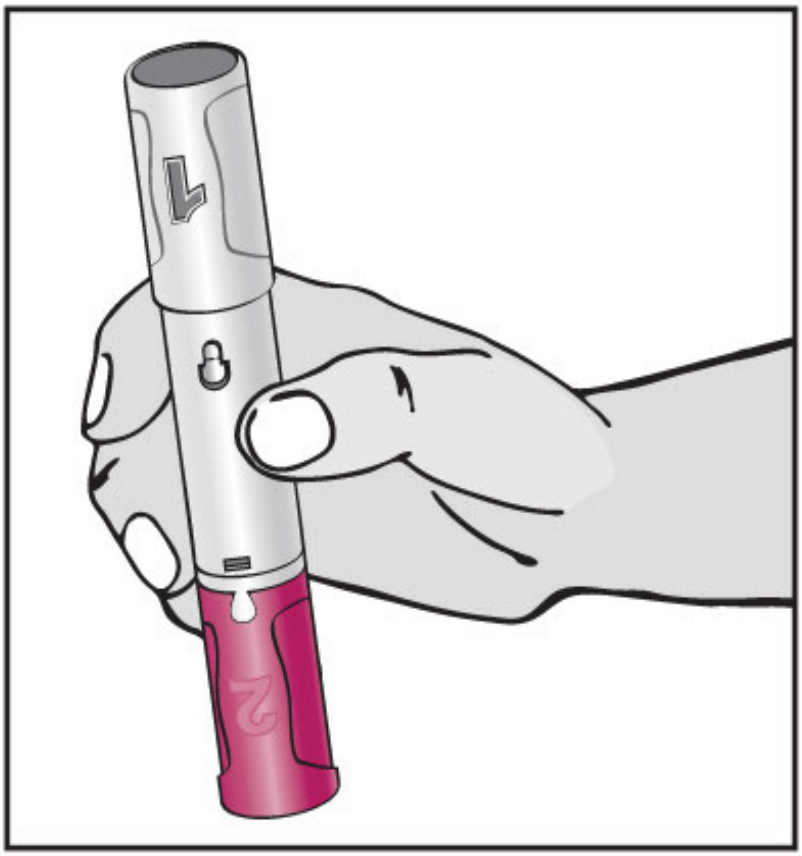
- **Do not** touch this area again before giving the injection. Allow the skin to dry before injecting. **Do not** fan or blow on the clean area.

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.

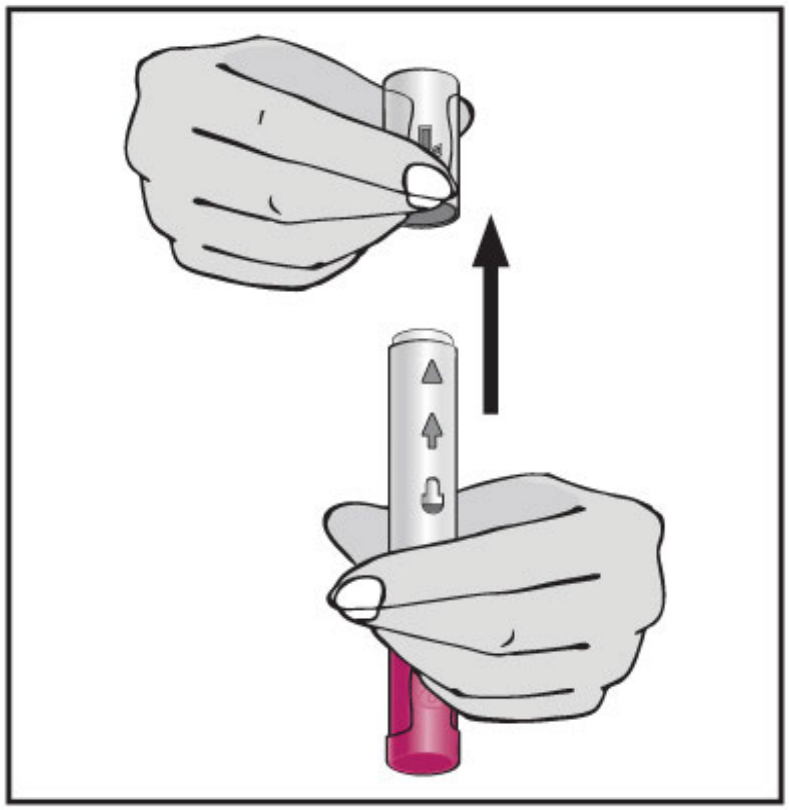
Figure E



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.

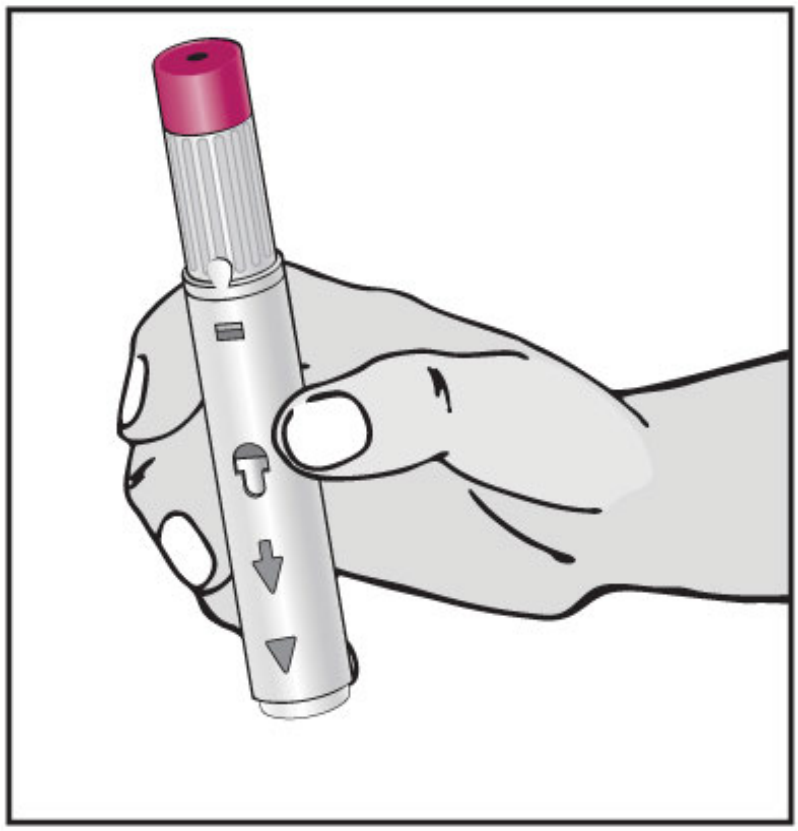
15. Remove the plum-colored cap (Cap # 2) from the bottom of the Pen by pulling it straight off (do not twist the cap). The Pen is now activated. Throw away the plum-colored cap.

- 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:

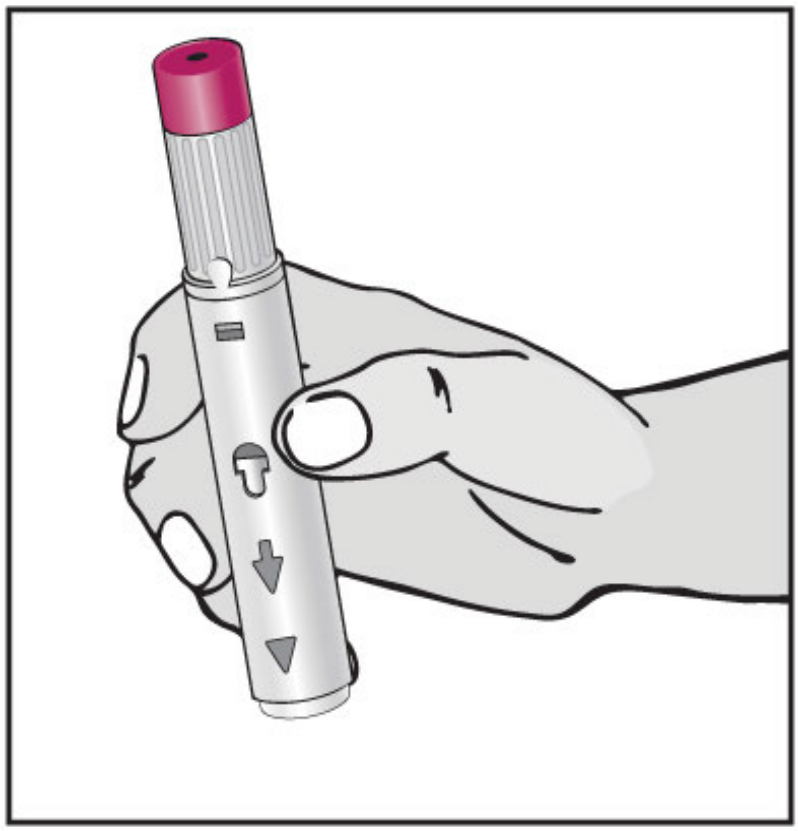
- Turn the Pen so the plum-colored activator button is pointed up. See Figure G.

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

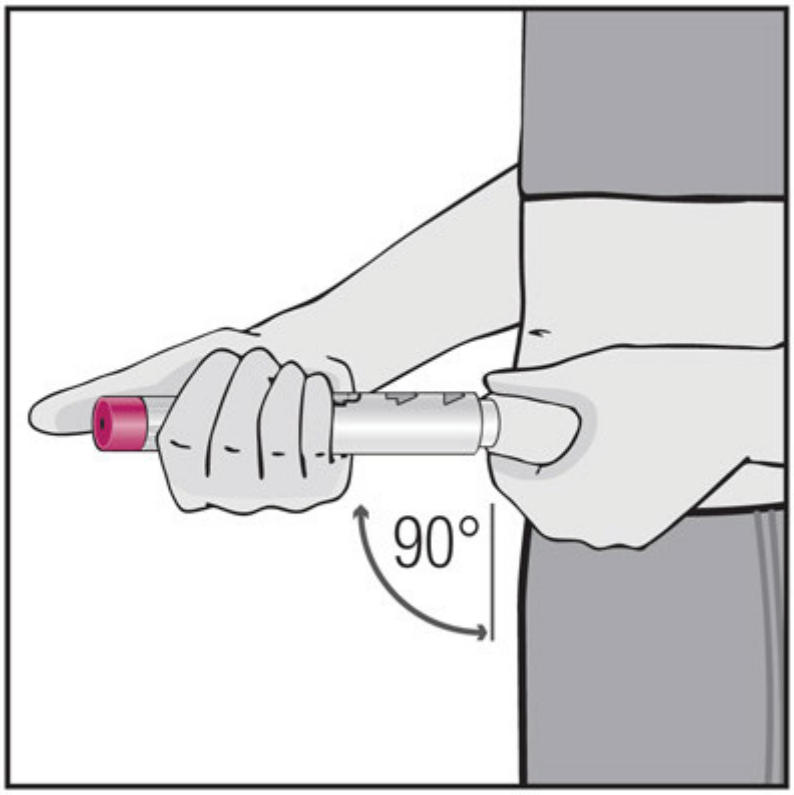
16. Position the Pen:

- 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.

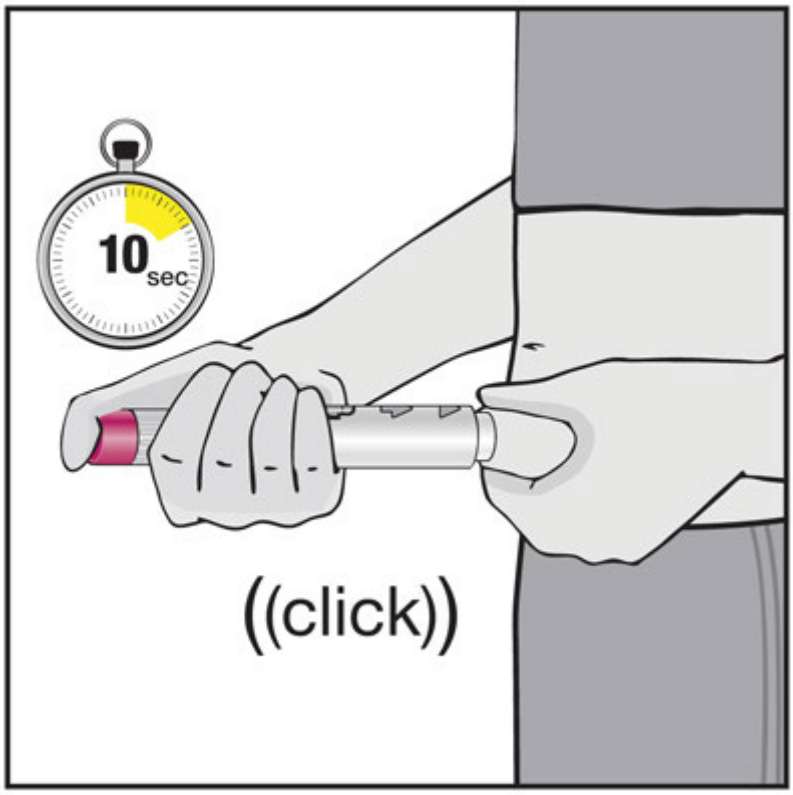
Figure J



18. Inject HUMIRA

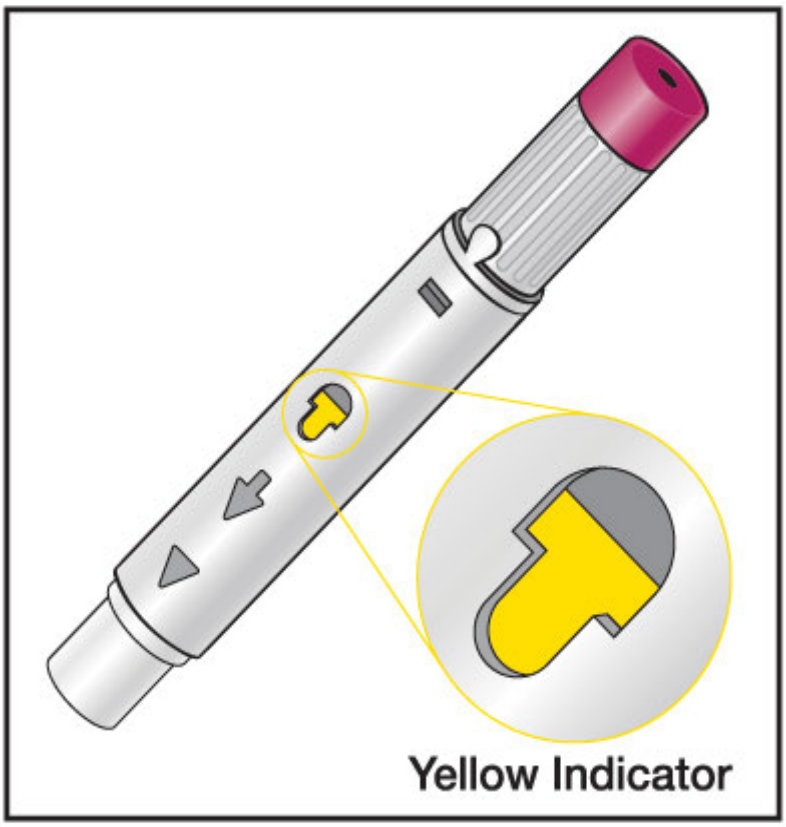
- With your index finger or your thumb, press the plum-colored activator button to begin the injection. Try not to cover the window. See Figure K.

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.

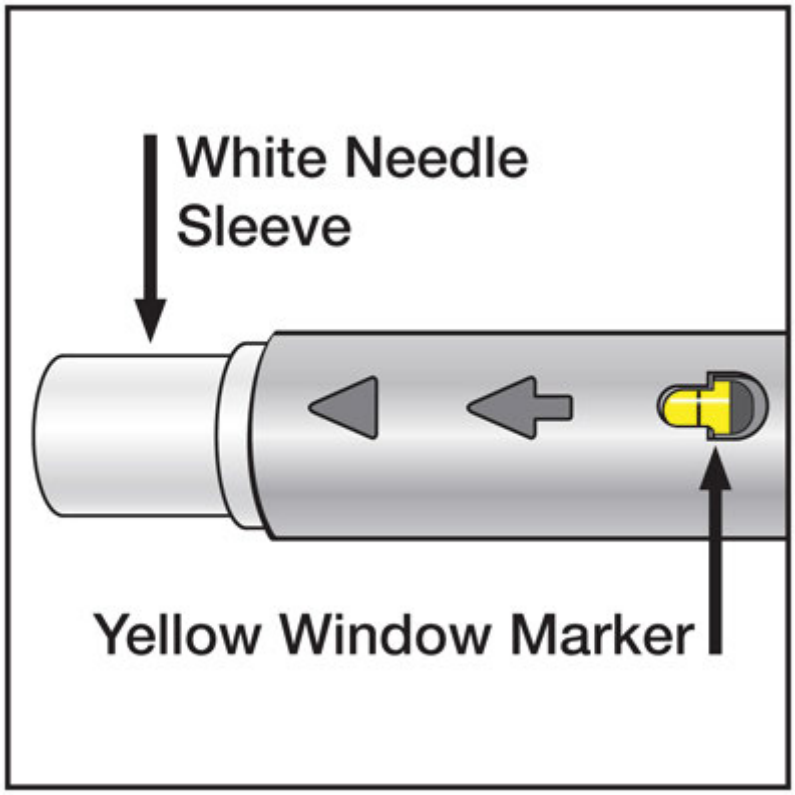
Figure L



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.

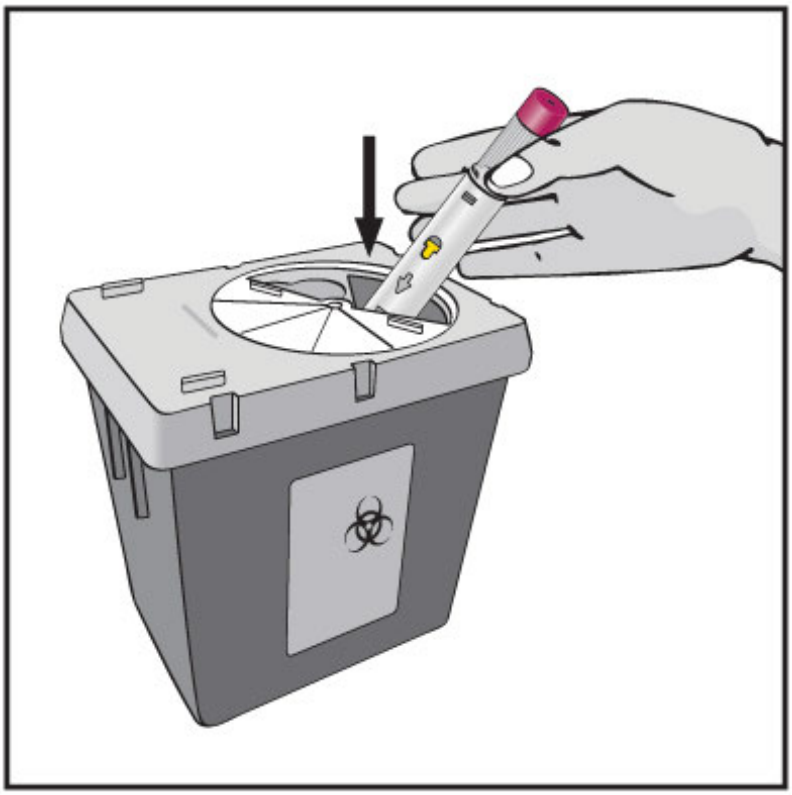
20. Dispose of your used HUMIRA Pen. See the section **"How should I dispose of the used HUMIRA Pen?"**

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.

Manufactured by:

AbbVie Inc.

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

US License Number 1889

Revised: 9/2014

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 and have read and understand this Instructions for Use. 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. It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time. 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.**

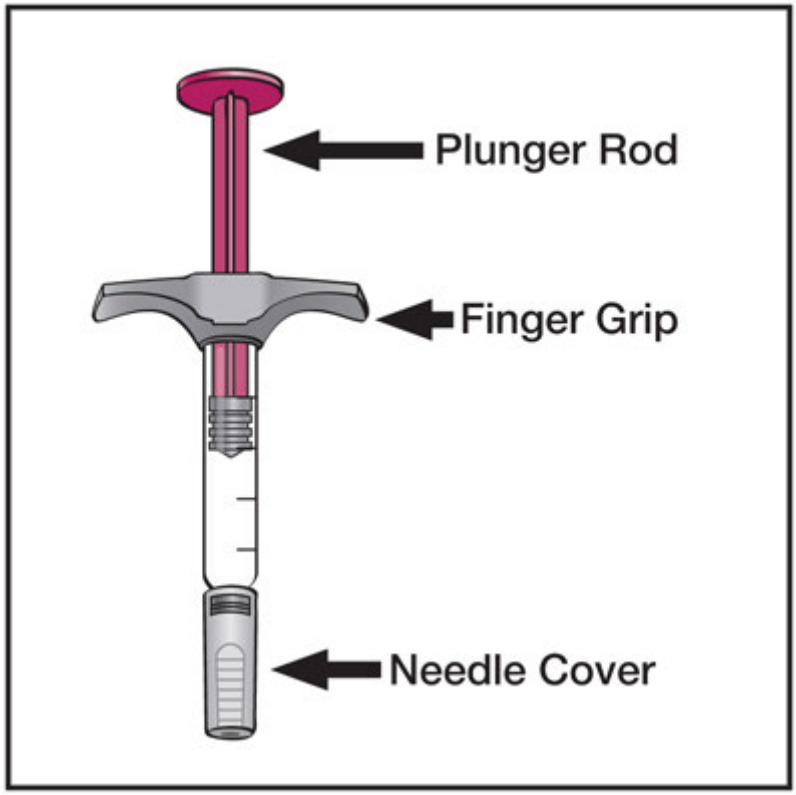
Gather the Supplies for Your Injection

- You will need the following supplies for each 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)
    - 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 or 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 this 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.

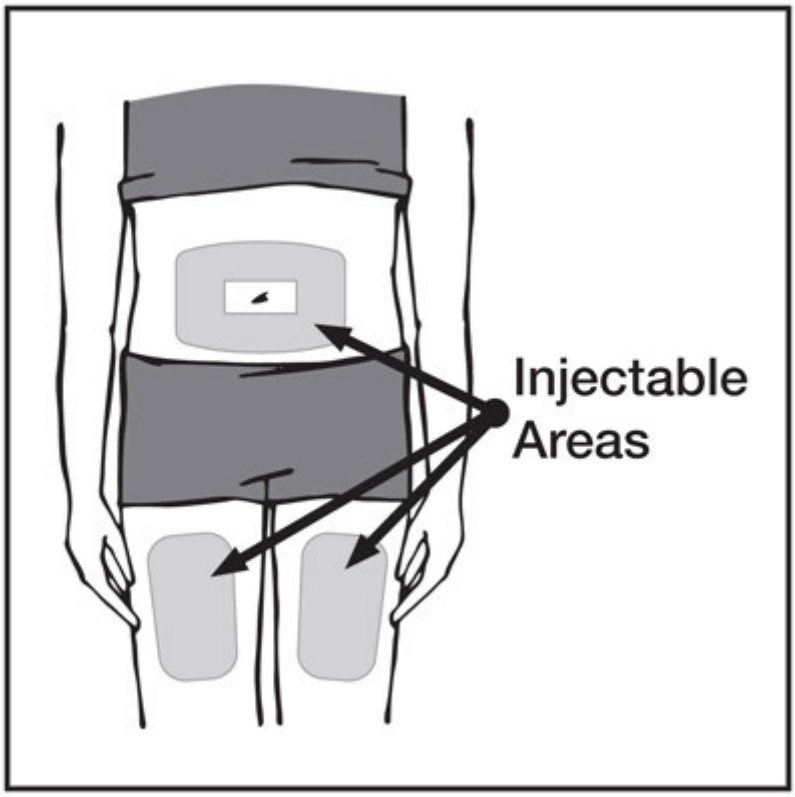
Choose the Injection Site

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.

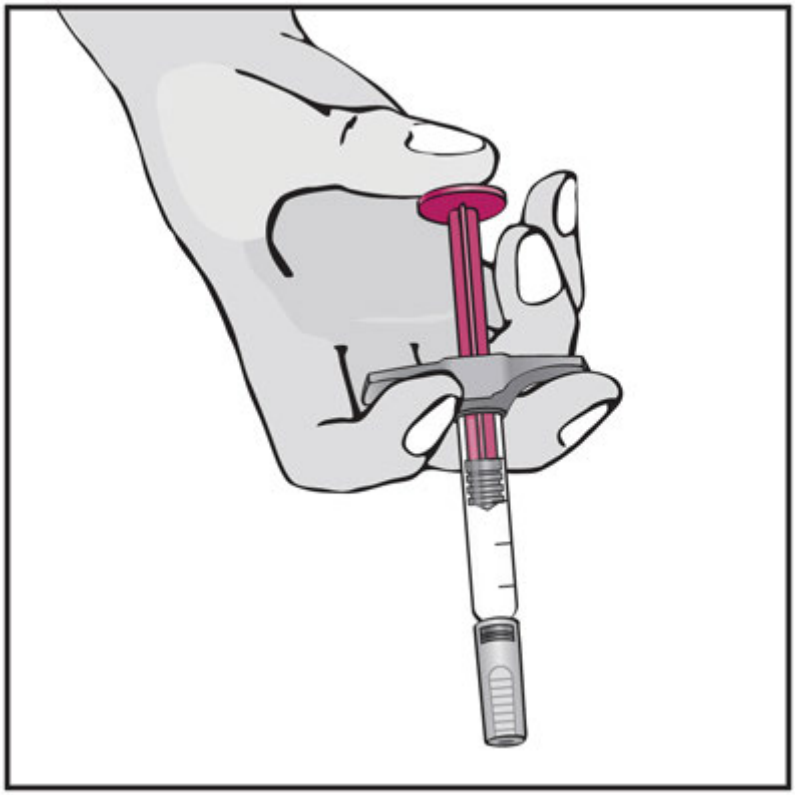
6. Do **not** touch this area again before giving the injection. Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Prepare the Syringe and Needle

7. Check the fluid level in the syringe:

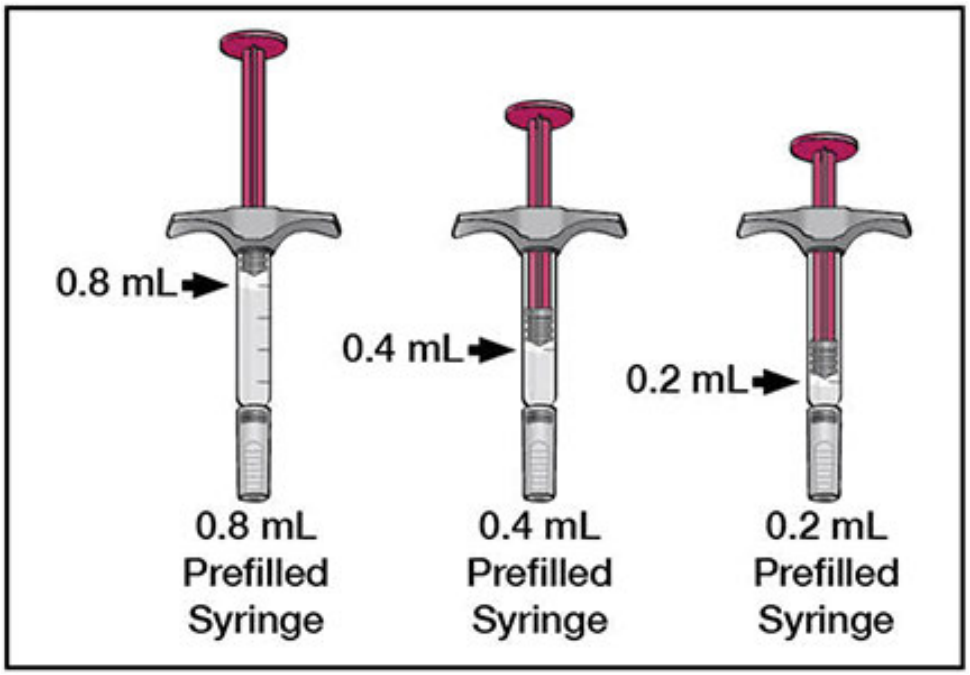
- Always hold the prefilled syringe by the body of the syringe. Hold the syringe with the covered needle pointing down. See Figure C.

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. See Figure D.
    - 0.4 mL line for the 20 mg prefilled syringe. See Figure D.
    - 0.2 mL line for the 10 mg prefilled syringe. See Figure D.

Figure D

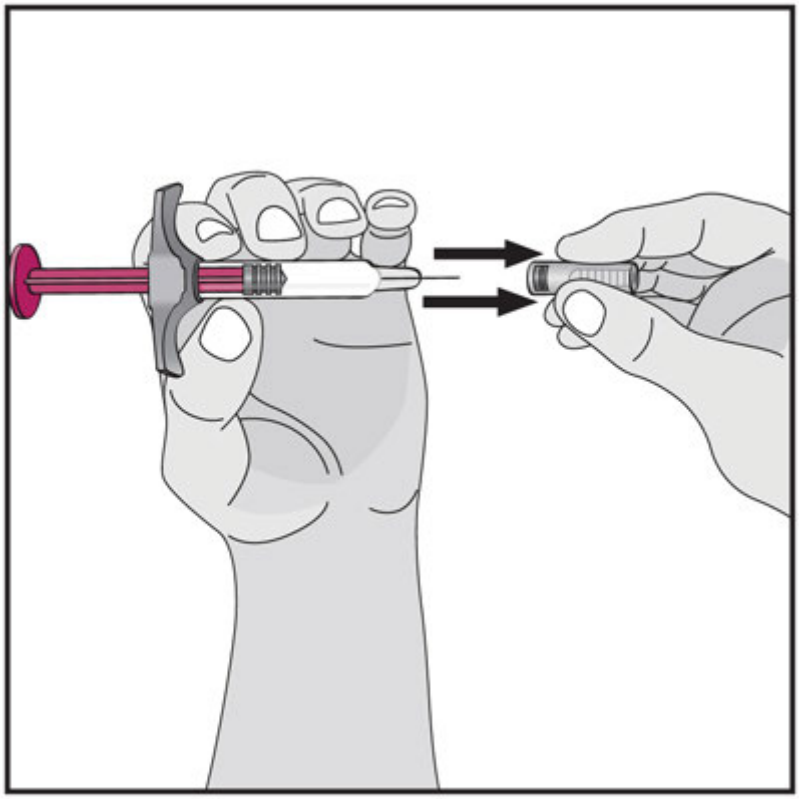


8. The top of the liquid may be curved. If the syringe does not have the correct amount of liquid, **do not use that syringe**. Call your pharmacist.

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.

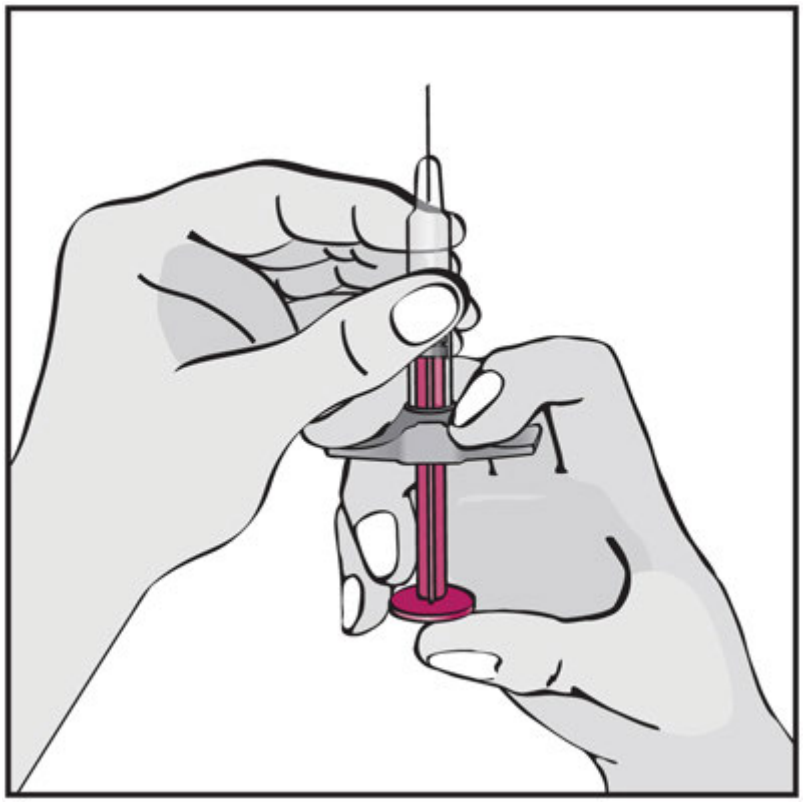
Figure E



- 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



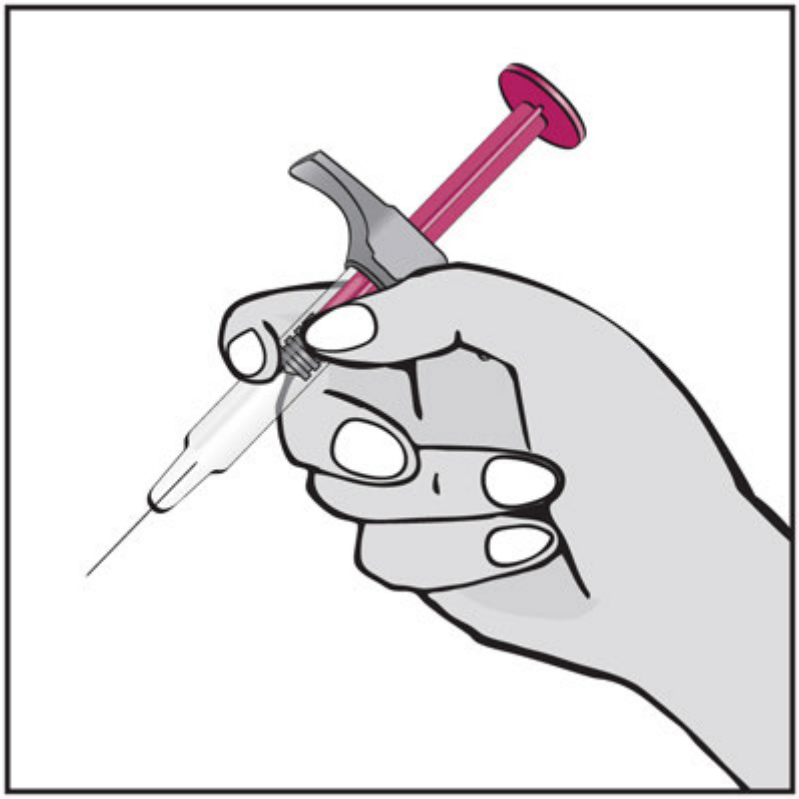
- You may see a drop of liquid at the end of the needle. This is normal.

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



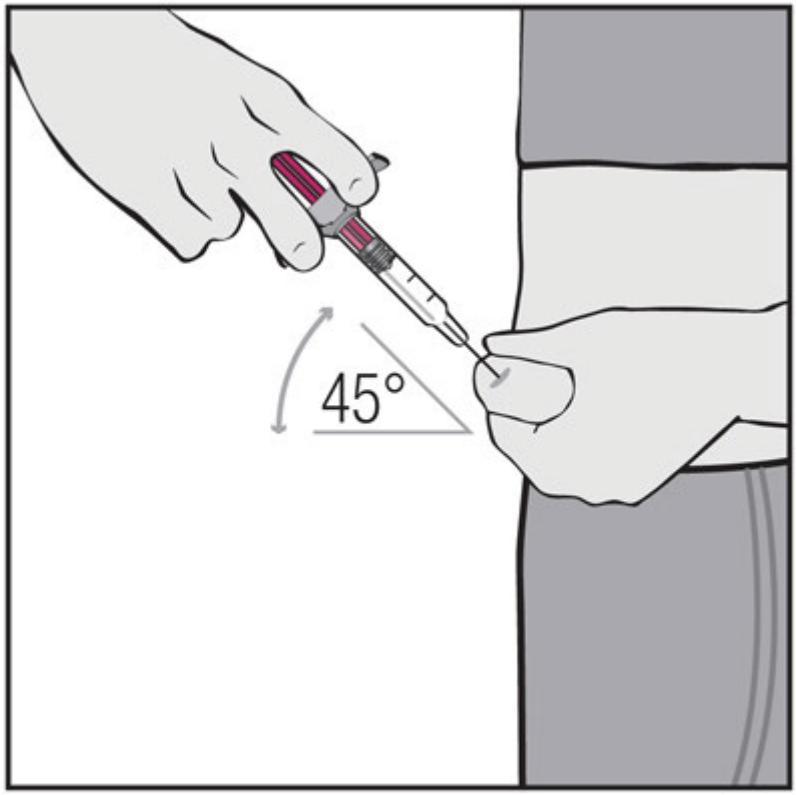
- **Do not** pull back on the plunger at any time.
- With your other hand, gently squeeze the area of the cleaned skin and hold it firmly. See Figure H.

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

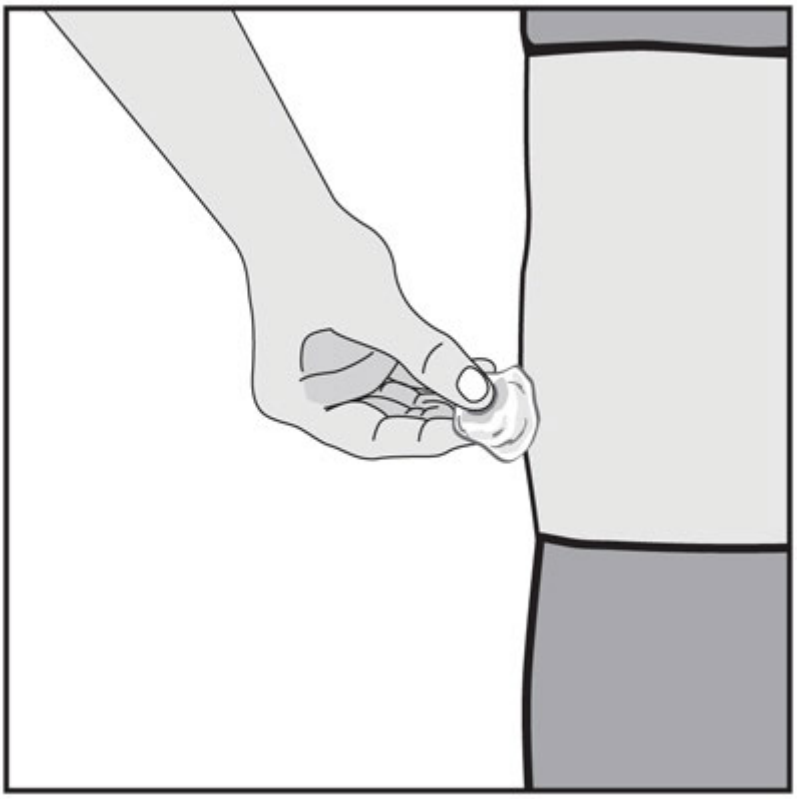


- After the needle is in, let go of the skin. Pull back gently on the plunger.

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.

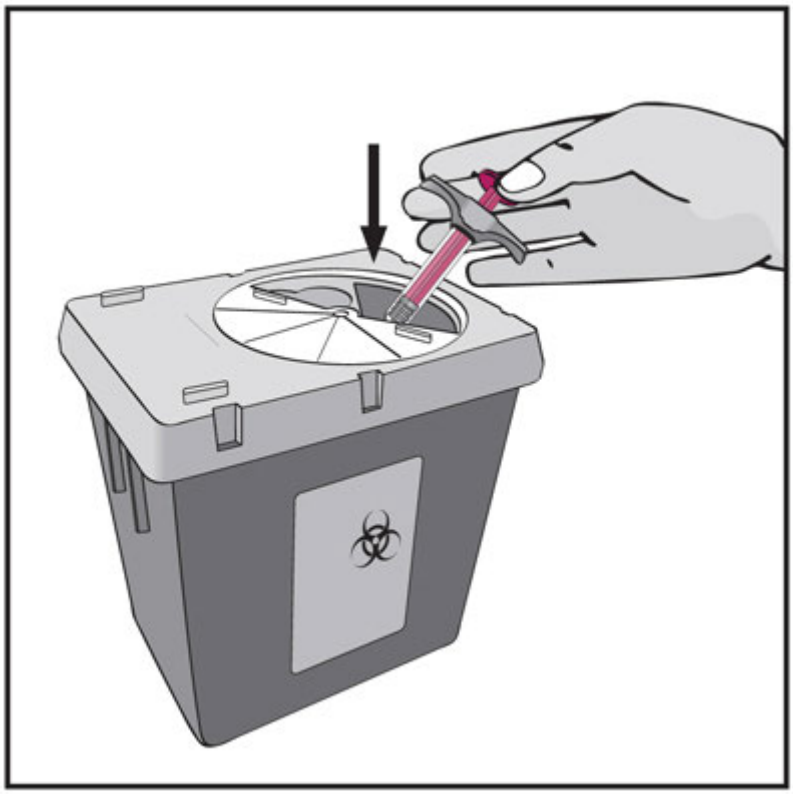
13. Throw away the used prefilled syringe and needle. See **"How should I dispose of used prefilled syringes and needles?"**

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.

Manufactured by:

AbbVie Inc.

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

US License Number 1889

Revised: 9/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

SUMMARY REVIEW

Deputy Director Review
sBLA 125057/356
Humira® (adalimumab)
September 23, 2014

Summary Review for Regulatory Action

Date	September 23, 2014
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA #	*BLA 125057/356*
Applicant Name	Abbvie
Date of Submission	August 29, 2013
PDUFA Goal Date	September 29, 2014
Proprietary Name / Established (USAN) Name	Humira® / Adalimumab
Dosage Forms / Strength	Current: ▪ single-use pen: 40 mg (0.8 mL) ▪ single-dose prefilled glass syringe: 20 mg (0.4 mL); 40 mg (0.8 mL) ▪ single use glass vial (for institutional use only): 40 mg (0.8 mL) Proposed: single-dose prefilled glass syringe: 10 mg (0.2 mL)
Proposed Indication(s)	inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Benjamin Vali, MS Freda Cooner, Ph.D.
Medical Officer Review	Marjorie Dannis, MD
Quality Quality Micro	Jun Park Reyes Candau-Chacon
OPDP	Meeta Patel
OSI	Susan Leibenhaut, MD
PMHS	Miriam Dinatale Ethan Hausman, MD
DMEPA	Teresa McMillan
CDRH Compliance	Viky Verna
Clinical Pharmacology	Jee Eun Lee, Ph.D. Jie Wang, 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
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

Signatory Authority Review Template

1. Introduction

In this SE5 efficacy supplement (addition of pediatric use and dosing information) to the BLA (sBLA) for Humira® (adalimumab), the applicant proposes to market Humira® (adalimumab) for the following indication in children:

1) for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4) (b) (4)

Humira® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Humira® 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 Humira® with labeling revision for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who (b) (4). 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-alpha 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 Study M06-806 and Study M06-807, a long term open-label tolerability study enrolling patients who had a clinical response from first study. The objective of these studies was to demonstrate the safety and efficacy of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD and to assess the pharmacokinetics (PK) of Humira® administered by subcutaneous (SC) injection.

Study Design

This study was a multi-center, randomized, double-blind, safety, efficacy and PK study designed to demonstrate the effectiveness of two dosage regimens of Humira® in the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD. This study contained two dosing periods, a 4-week open-label induction period, and a 48-week double-blind period. Subjects who experienced a flare or non−response following an 8-week course of double-blinded weekly therapy could be switched to open label weekly therapy. See **Figure 1** below for a pictorial of the flowchart and Study design for this trial:

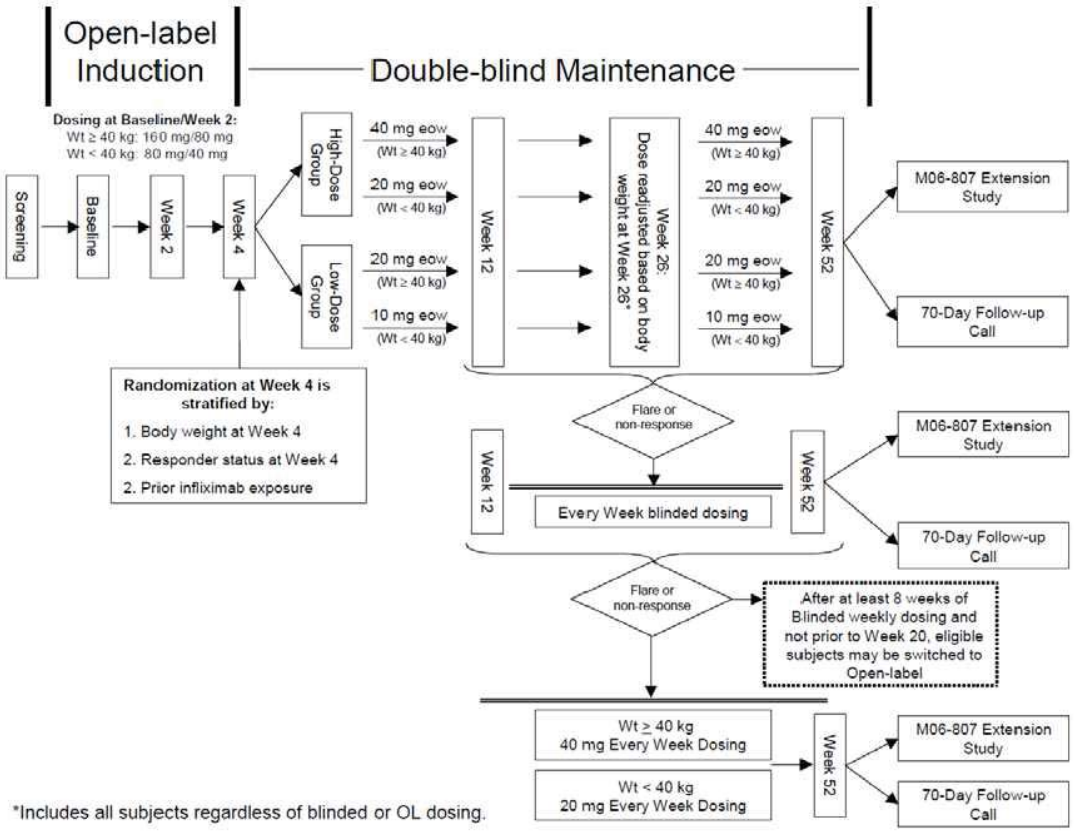


Figure 1. Schematic of study design (Source: *Figure 1, page 117, Adalimumab M06-806 Clinical Study Report, R&D/10/605)*

Reproduced from CDTL memorandum, Dr. Rajpal

Approximately 180 pediatric subjects between the ages of 6 and 17, inclusive, with a diagnosis of moderate to severe CD (defined by a Pediatric Crohns Disease Activity index (PCDAI >30 who had failed conventional therapy for CD (as defined in the Inclusion Criteria) or who have previously lost response or had adverse reactions to infliximab and with confirmation of CD by endoscopic or radiological evaluation, were enrolled at approximately 50 sites in the United States, Canada, and Europe. Enrollment was dependent on meeting all inclusion and none of the exclusion criteria. At least 80 subjects were ≥ 13 years old at Baseline and one-third to one-half of the study population were subjects who had previously lost response or had adverse reactions to infliximab.

The open-label induction dose was dependent on the subject's baseline body weight. If a subject was ≥ 40 kg, they received 160 mg and then 80 mg adalimumab at Weeks 0 and 2, respectively. If a subject was < 40 kg, they received 80 mg and then 40 mg at Weeks 0 and 2, respectively. At Week 4, subjects were stratified according to their Week 4 body weight, Week 4 responder status (clinical response was defined as PCDAI decrease ≥ 15 points from the Baseline score), and their prior exposure to infliximab, and randomized

1:1 to one of two maintenance treatment groups. One dose cohort received either 40 mg adalimumab SC (if BW ≥ 40 kg) or 20 mg adalimumab SC (if BW< 40 kg) per dose every other day (eow), while the other dose cohort received either 20 mg adalimumab SC (if BW ≥ 40 kg) or 10 mg adalimumab SC (if BW < 40 kg) per dose eow. Subject body weight taken at Week 26 was used to readjust the maintenance dosing regimen for subjects whose body weight had increased from < 40 kg to ≥ 40 kg during the study.

The duration of the study was up to 65 weeks, which included a 1-week to 3-week Screening period, an OL Induction period, a Maintenance period, and a 70-day follow-up phone call for all subjects who either terminated early from the study or did not rollover into the extension study (Study M06-807).

In addition to the PCDAI, the Crohn's Disease Activity Index (CDAI) was measured in subjects' ≥ 13 years of age. Additional efficacy assessments, as well as safety and PK measurements were performed throughout the study.

The issues related to this primary endpoint will be discussed below. Study M06-807 was a long term open label tolerability study enrolling patients who had a clinical response from first study.

This Summary review will discuss the sufficiency of evidence of clinical benefit supported by the data in this application to establish that Humira® (adalimumab) is effective and safe for the treatment for children. My review will focus on the salient issues related to this risk/benefit assessment for the indication of reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4) (b) (4) In summary the data in this application do establish that Humira (adalimumab) is effective and safe for the treatment of Crohns disease in children. I have concluded that there is sufficient evidence of clinical benefit, which results in a recommendation of approval of this supplement.

2. Background

The reader is referred to Dr. Dannis' 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). Humira® (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 SE5 efficacy supplement (addition of pediatric use and dosing information) to the BLA (sBLA) for Humira® (adalimumab), the applicant proposes to market Humira® (adalimumab) for the following indication in children for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4)

3. CMC

The reader is referred to the CMC Review by Jun Park for further details. Briefly, Humira® (adalimumab) is currently licensed at 50 mg/mL in multiple formats including prefilled syringes at varying concentrations, prefilled pen and glass vial as delineated below:

- 40 mg/0.8 mL prefilled syringe
- 20 mg/0.4 mL prefilled syringe
- 20 mg/0.4 mL prefilled pen
- 40 mg/0.8 mL glass vial (institutional use only)

The applicant also provided data to support the 10 mg/0.2 Prefilled syringe format. The formulation and container closure of the drug product in the proposed 10 mg/0.2mL PFS presentation is identical to the approved Humira® (adalimumab) presentations. A description of the manufacturing process for the 10 mg/0.2 mL PFS in the submission included testing results for the characterization/comparability, process validation, batch release, and stability. It should be noted that there does not appear to be any clinical experience with the 10 mg PFS. The sponsor is relying upon clinical data for a 10 mg maintenance dose that is based on either the 50 mg/mL vial or a 25 mg/mL vial.

The CMC Reviewer recommended Approval of the supplement.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the review of Jee-Eun Lee, Ph.D. for further details. The dosing recommendation for Humira® (adalimumab) in this indication is illustrated below in **Table 1** and discussed below in revisions to the Humira® (adalimumab) label:

Table 1: Dosing regimen for management of Moderate-Severe Crohns Disease in children

Patients	Induction Dose	Maintenance Dose (Starting at Week 4)
		(b) (4)
17 kg (37 lbs) to < 40 kg (88 lbs)	80 mg at Week 0, 40 mg at Week 2 (80/40 induction regimen)	20 mg EOW (b) (4)
≥ 40 kg (88 lbs)	160 mg at Week 0.80 mg at Week 2 (160/80 induction regimen)	40 mg EOW

Dr. Lee discusses the rationale for these labeling recommendations based on the evidence supporting extrapolation of efficacy from adults to children. It should be noted that the primary efficacy endpoint was rate of clinical remission (defined as PCDAI ≤ 10) at Week 26. Because Study M06-806 did not include a placebo control group, the measure of trial success was to be the comparability of efficacy based on an external comparison with data from adults following 40 mg EOW dosing regimen (Study M06-404). The primary efficacy endpoint was modified to assess the success of the trial by comparing CDAI clinical remission at Week 26 to CDAI clinical remission at Week 24 in and adult trial (Study M06-404). For the external comparison, correlations between CDAI scores and PCDAI scores in patient's ≥13 years of age were evaluated to obtain conversion factors for patient's ≥ 13 years of age and < 13 years for adjustment of PCDIA. The adjusted PCDAI clinical remission at Week 26 was then compared to CDAI clinical remission in adults at Week 24. These issues are also discussed below in Section 7, Clinical/Statistical-Efficacy.

For the induction period, support for extrapolation is established based on the data reviewed by Dr. Lee from the clinical trial. The exposure-response relationship of Humira® (adalimumab) concentration to remission was not demonstrated as shown in **Figure 1** in the CDTL memorandum. As noted by Dr. Rajpal, the Clinical Pharmacology Reviewers noted that trough concentrations and the proportion of patients in clinical remission at Week 4 were comparable with those in adults following the 160/80 mg dosing regimen. See **Table 2** below reproduced from Dr. Rajpal memorandum for these data:

Table 2. Summary of Concentration of Adalimumab and Clinical Remission at Week 4 by Treatment Group and Population

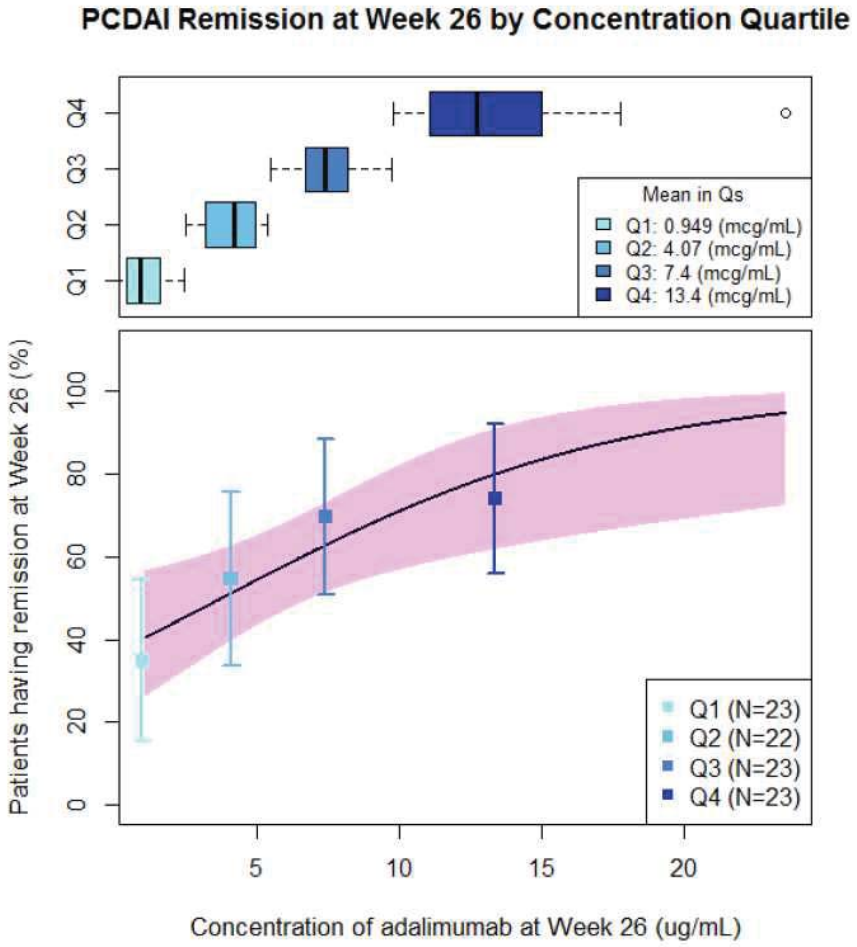
Population	Subgroup	Dose	Ctrough (mcg/mL, Mean ± SD)	Clinical Remission at Week 4
Pediatrics	< 40 kg (N=54)	80/40 mg	10.57 ± 6.00	13/54 (24.1% [12.7, 35.5])
	≥ 40 kg (N=113)	160/80 mg	14.97 ± 6.94	31/113 (27.4% [19.2, 35.7])
Adults (M02-403)	N=76	160/80 mg	12.61 ± 5.25	27/76 (35.5%)
Adults (M04-691)	N=159	160/80 mg	12.63 ± 6.04	34/159 (21.4%)

(Reviewer's analysis for pediatrics. Source for adult data: M02-403 CSR Table 20, M02-403 PK Report page 4, M02-691 Table 16, M02-691 PK Report page 5)

Table above is taken from Page 13 of the Clinical Pharmacology Review.

For the maintenance period after induction of 4 weeks, specifically, one sees the PCDAI remission at week 26 is related to the concentration quartile reflective of higher remission rate with higher Humira® (adalimumab) concentrations (**Figure 2, below**).

Figure 2: PCDAI Remission at Week 26 by Concentration Quartile



It is clear that the exposure-response of adalimumab at week 26 demonstrates a dose response relationship which is reflected in the subgroup analysis in the **Table 3** below. The serum concentration **Ctrough** of Humira® (adalimumab) that is higher is progressively associated with a higher rate of clinical remission at week 26.

Table 3: Subgroup Analysis of Ctrough and Clinical remission at Week 26:

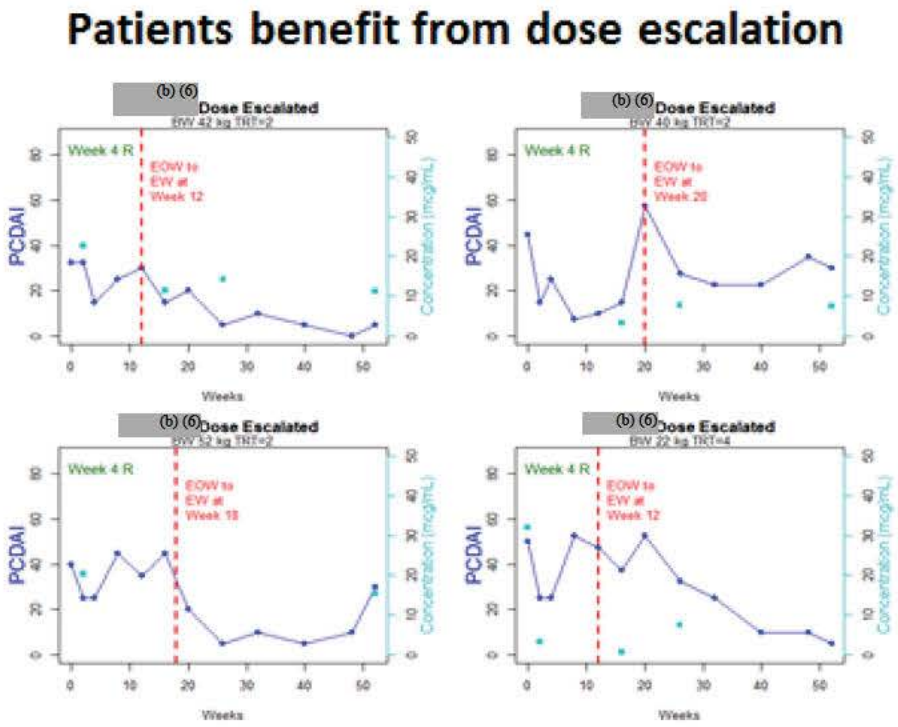
	Subgroup	Ctrough (Mean ± SD)	Clinical Remission at Week 26
ER Dataset* (N=91)	Q1 (N=23)	0.95 ± 0.73	8/23 (34.8% [15.3, 54.2]
	Q2 (N=22)	4.07 ± 0.91	12/22 (54.5% [33.7, 75.4]
	Q3 (N=23)	7.4 ± 1.13	16/23 (69.6% [50.8, 88.4]
	Q4 (N=23)	13.4 ± 3.25	17/23 (73.9% [56.0, 91.9]

It is critical to review these data in that there is a suggestion that week 4 induction levels were not maintained for achieving clinical remission in a percentage of patients except those patients represented in the highest exposures of the quartile 4 who had trough levels above 10 ug/mL. The relevance of other subgroups analyzed by Dr. Lee are potentially important; to this Signatory, the most critical determinant of efficacy either in the induction or maintenance period of treatment is putatively related to target therapeutic drug levels of Humira® (adalimumab). It would appear based on data presented in **Table 4** that there is a minimum concentration Ctrough above which ensures that there is a higher chance of remission from disease activity. For example, the highest doses of Humira® (adalimumab) tested resulted in higher Ctrough concentrations and concomitantly higher percentage of clinical remission at Week 26 (see **Table 4** below)

Table 4: Exposure Response and Clinical remission in Various Weight Groups Exposed to Different Humira dosing regimens

		Dose	Ctrough (Mean ± SD)	Clinical Remission at Week 26
	N		91 (42 missing)	133
ER dataset II (N=133; subjects who stayed with the original therapy until Week 26)	< 40 kg (N=39)	10 mg (N=19)	1.98 ± 1.41	5/19 (26.3% [6.5, 46.1])
		20 mg (N=20)	7.57 ± 3.62	8/20 (40.0% [18.5, 61.5])
	≥ 40 kg (N=94)	20 mg (N=47)	3.7 ± 2.71	20/47 (42.6% [28.4, 56.7])
		40 mg (N=47)	10.7 ± 4.6	23/47 (48.9% [34.6, 63.2])

This hypothesis of a relationship of serum concentration of Humira® (adalimumab) and clinical remission status has been evaluated through further analyses by Dr. Lee. After these analyses shown below, one concludes that there is not necessarily a specific therapeutic drug concentration cut-off of Humira® (adalimumab) associated with clinical remission. For example, in the pictorial below (**Figure 3)** and **Table 5**, Dr. Lee analyzed the benefit from dose escalation in 4 patients and their specific data. In two of the four subjects analyzed, serum concentrations of adalimumab were above 10 ug/ml, and still associated with lack of clinical remission.



1

Figure 3: Individual Patient Plots of Dose Escalation, PCDAI and Time

Cutoff 10 ng/mL

		Subject (N)	Dose escalated prior to Week 26 (N (%))	Dose escalated during Study (N(%))
Week 4	All	169	46 (27%)	79 (47%)
	>= 10 ng/mL	113	29 (26%)	48 (42%)
	< 10 ng/mL	56	17 (30%)	31 (55%)
Week 16	All	142	41 (29%)	76 (54%)
	>= 10 ng/mL	33	9 (27%)	15 (45%)
	< 10 ng/mL	109	32 (29%)	61 (56%)
Week 26	All	132	41 (31%)	66 (50%)
	>= 10 ng/mL	32	12 (38%)	15 (47%)
	< 10 ng/mL	100	29 (29%)	51 (51%)
Overall	All	178	46 (26%)	80 (45%)

Table 5: Analysis of PK Cutoff 10 mg/ml and Relationship to Dose Escalation

The rationale for the need for a 4-week induction period for the use of Humira® (adalimumab) for the treatment of pediatric CD remains unclear but adapted from the adult treatment regimen. The issue of higher doses utilized for the induction period for 4 weeks may be more important for reducing safety related drug reactions than sustaining efficacy as the data demonstrate that the need for dose escalation to EW dosing is prevalent in a population of children treated during this trial which support conclusion. Dose escalation was observed in a significant percentage of children in Study M06-806 as described in memorandum of Dr. Lee. Remission rates re reflected in Tables 10 and 11 in Dr. Lee's review and suggest the maintaining a certain concentration may impact on Clinical remission (CR) and Clinical response. These issues would need to be evaluated prospectively for further clarification but will not be requested as a Post-marketing commitment since there is not the level of evidence to support it at the current time.

Overall the Clinical Pharmacology reviewer recommended approval for the indication. The summary basis of approval rests on to this Reviewer support for extrapolation and dose response. Further details are discussed by Dr. Lee and Rajpal in their memoranda.

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 the clinical review of Dr. Dannis and 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 Humira® (adalimumab). My comments will be focused on the use of the PCDAI as an efficacy endpoint and the study design used in this registration study and the support for this indication for Humira® (adalimumab).

a. Use of the PCDAI as an Efficacy Endpoint: Its Advantages and Disadvantages:

The primary efficacy endpoint was rate of clinical remission (defined as PCDAI ≤ 10) at Week 26. Because Study M06-806 did not include placebo control group, the measure of trial success was to be the comparability of efficacy based on an external comparison with data from adults following 40 mg EOW dosing regimen (Study M06-404), the adult pivotal trial. The primary efficacy endpoint was modified to assess the success of the trial by comparing PCDAI clinical remission at Week 26 to CDAI clinical remission at Week 24 in an adult trial (Study M06-404). For the external comparison, correlations between CDAI scores and PCDAI scores in patient's ≥13 years of age were evaluated to obtain conversion factors for patient's ≥ 13 years of age and < 13 years for adjustment of PCDIA. The adjusted PCDAI clinical remission at Week 26 was then compared to CDAI clinical remission in adults at Week 24. In addition the use of the PCDAI for assessment of the efficacy endpoint is based on historical use in Remicade trials for the registration of Remicade for the treatment of pediatric Crohn's disease. The PCDAI is calculated from a series of biomarkers and clinical measurements that have been developed with a scoring algorithm as pictured below in **Figure 5**:

Figure 5: PCDAI Assessments and Score Calculation

		Score
1. Abdominal pain rating		
- None	= 0 p	
- Mild - Brief, does not interfere with activities	= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal	= 10 p	
2. Stools (per day)		
- 0 – 1 liquid stools, no blood	= 0 p	
- Up to 2 semi-formed with small blood, or 2 – 5 liquid	= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	= 10 p	
3. Patient Functioning, General Well-Being		
- No limitation of activities, well	= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par	= 5 p	
- Frequent limitation of activity, very poor	= 10 p	
LABORATORY		**Score**
4. HCT: Male and female ≤ 10 years: ≥ 33 = 0 p; 28 – 32 = 2.5 p; < 28 = 5 p	Male 11 – 14 years: ≥ 35 = 0 p; 30 – 34 = 2.5 p; < 30 = 5 p	
Female 11 – 19 years: ≥ 34 = 0 p; 29 – 33 = 2.5 p; < 29 = 5 p	Male 15 – 19 years: ≥ 37 = 0 p; 32 – 36 = 2.5 p; < 32 = 5 p	
5. ESR (mm/hr) < 20 = 0 p; 20 – 50 = 2.5 p; > 50 = 5 p		
6. Albumin (g/dL) ≥ 3.5 = 0 p; 3.1 – 3.4 = 5 p; ≤ 3.0 = 10 p		
EXAMINATION		**Score**
7. Weight - Weight gain or voluntary weight stable/loss	= 0 p	
- Involuntary weight stable, weight loss 1% – 9%	= 5 p	
- Weight loss ≥ 10%	= 10 p	

The pCDAI includes 3 items derived from the clinical history (abdominal pain, number of stools, and well-being) dependent on a one-week recall. The pCDAI has 5 examination items including measures of weight gain, height velocity, the findings associated with an abdominal examination, presence and severity of perirectal disease, and a grading of extra-intestinal manifestations. The laboratory items include hematocrit (with separate grading for four child and adolescent groups), erythrocyte sedimentation rate, and serum albumin. Items are scored on a 3-point scale (scores 0, 5 or 10, except

for hematocrit and erythrocyte sedimentation rate, which carry a lower weight scores of 0, 2.5, or 5). Total scores can range from 0 to 100, with higher scores indicating more active disease. Since physicians obtain and interpret the information, the pCDAI is a proxy report, not a Patient related outcome or Observer related Outcome (ObsRO). Additionally, the source of the information, i.e., whether it is the child or caregiver, is unclear and can be variable. The extent to which the physician completing the assessment includes his/her own interpretation is unclear. The lack of standardization in measurement introduces variability and results in concepts of measurement (disease activity, response and remission) being variably defined. Furthermore, unobservable concepts such as pain can only be assessed via direct report; if direct report is not feasible; such concepts must be assessed indirectly based on observable signs. The ability of the individual to ignore or over-report pain (pCDAI abdominal pain item) may be related to various other factors unrelated to the disease (e.g. psychosocial status of adolescent patients). In addition, the pCDAI lacks an adequate age-appropriate interviewer script and response rating criteria for the physician interviewer.

Several items include multiple concepts within a single item. For example, pain severity, pain interference and pain duration are combined in a single item. Similarly, stool frequency, consistency and presence of blood are also combined within a single item. Additionally, general well-being item in patient functioning is vague and attempts to measure a complex concept (e.g., well-being) using a single global item. The validity of a one-week recall period is uncertain for concepts that can vary from day to day such as pain as well as stool frequency and consistency.

Despite these weaknesses, the Division has accepted this endpoint as a suitable outcome measure previously for the registration trial for Remicade® (infliximab). Looking forward to future registration trials in adults and pediatric patients, the DGIEP has made significant strides towards modification of endpoints in IBD to focus on co-primary endpoints, comprised of evaluation of endoscopic disease activity (reflected MOA and activity of a drug to induce remission and response) and clinical signs and symptoms. The application of these approaches to children requiring new therapeutic agents targeting IBD await the execution of properly conducted trials in children with novel therapies. The reader is referred to the public discussions that have been executed through the Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II)" conference sponsored by DGIEP and the FDA held October 21-22, 2013. The purpose of this workshop was to provide a forum for academia, industry, and FDA to discuss the issues related to endpoints that can support drug development in pediatric and adult inflammatory bowel diseases. Collaboration among stakeholders is essential to moving forward in developing the best therapies for our patients with IBD. Discussions focused on Crohn's disease on Day 1 and Ulcerative Colitis and Crohn's disease on Day 2 of GREAT II. Topics included the definitions of patient reported outcomes (PROs) and observer reported outcomes (ObsROs), strengths and weaknesses of the CDAI/PCDAI, and the roles of endoscopy, imaging, and mucosal healing in assessing disease activity and treatment outcomes.

During discussion sessions, many participants endorsed the concept that treatment benefit should be measured through a combined evaluation of symptoms that accurately reflect disease activity and an endoscopic assessment, in both adult and pediatric clinical trials. Abdominal pain and stool frequency are symptoms/signs of Crohn's disease that can be measured. In ulcerative colitis, rectal bleeding and stool frequency were signs participants identified for evaluation. Discussants noted that central reading could decrease variability among investigators for endoscopic assessment in clinical trials intended to support approval of new drugs. Ideally, a common efficacy measure would be used in adult and pediatric IBD clinical trials. However, many participants also noted that growth is important to evaluate in pediatric patients with IBD. Although efficacy may be extrapolated from adult data in certain circumstances, dose-finding and safety data cannot be extrapolated; therefore, appropriately designed pediatric trials are key to obtain meaningful information on appropriate dose and safety in pediatric patients.

b. Study Design and the Use of the External Comparisons using "Adjusted PCDAI Remission as Supportive Evidence of Efficacy

The Sponsor in this study design utilized a comparison of high and low dose Humira® (adalimumab) regimens as discussed above in Background. Data presented in this application used a reference to the CDAI calculated value only for children greater than age 13 years in the clinical trial. The weakness of this approach of extrapolating efficacy from adult endpoints results from a comparison of adult and pediatric endpoints derived differently. I do not concur with Dr. Rajpal' s attestation reiterating the position in the Clinical TL memo for Remicade for Pediatric CD sBLA: "…the PCDAI criteria for remission appeared to be a 'higher bar' compared to the CDAI criteria. In that Memo, the Clinical Team Leader further concluded: "…it appears reasonable to interpret the results of the REACH Study as showing that the response rates for Remicade in pediatric Crohn's disease are at least as high as the rates for Remicade in adult Crohn's disease." The multiple weaknesses of the pCDAI as a clinical endpoint are discussed below.

Dr. Rajpal notes that "If one considers the PCDAI criteria for remission to be a 'higher bar' compared to the CDAI criteria for remission (see Section 7.3.6), then the results above suggest that the response rates for Humira in pediatric Crohn's disease are at least as high as the rates for Humira in adult Crohn's disease." This logic of ascribing relevance to a non-controlled study of dose ranging does not have relevance in the absence of statistical difference. As shown below in **Table 6**, the results are not statistically different, p<.075:

Table 6: Primary Endpoint: Week 26 Clinical Remission (Study M06-806) (Study M02-404 Adult CD data included for descriptive comparison)

	Study M06-806				Study M02-404
	Low Dose* 20 or 10 mg eow N = 95 n/N (%)	High Dose# 40 or 20 mg eow N = 93 n/N (%)	Treatment Difference (95% CI)	p-value	40 mg eow N=260
Week 26					
Clinical Remission†	27/95 (**28.4%**)	36/93 (**38.7%**)	**10.3%** (-3.1%, 23.7%)	0.075	87/260 (**33.5%**)

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
†Clinical remission defined as PCDAI ≤ 10 (for Study M06-806 data); Clinical remission defined as CDAI ≤ 150 (for Study M02-404 data)
Study M06-806 results in table above are taken from the Clinical Review. Source: Sponsor's response to IR July 31, 2014. Study M02-404 results are taken from Page 236 of the M06-806 Clinical Study Report.

Reproduced from CDTL Memorandum, Dr. Rajpal

The problems associated with this clinical program rest on the difficulty in identifying the appropriate and effective dose for children. Based on the evidence used to approve Remicade for management of CD in children, it has become standard to accept that extrapolation can be used to support efficacy in pediatric CD. Despite Dr. Rajpal review of the extrapolation algorithm interpreted correctly in the CDTL memorandum, I am concerned with the lack of statistical differences between the doses tested to ensure that there was adequate dose-ranging study in children to select dose(s) that achieve the target PD effect. The body of evidence though supports the extrapolation algorithm as outlined by Dr. Rajpal.

Supportive evidence of a PD effect is noted by the analysis of the first three ranked secondary endpoints as shown below in **Table 7** which reflect significance only for clinical response at week 52.

Table 7: First Three Ranked Secondary Endpoints (Study M06-806)

	Study M06-806			
	Low Dose* (20 or 10 mg eow) N = 95 n/N (%)	High Dose# (40 or 20 mg eow) N = 93 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Response§	46/95 (**48.4%**)	55/93 (**59.1%**)	**10.7%** (-3.4%, 24.9%)	0.073
Week 52				
Clinical Remission‡	22/95 (**23.2%**)	31/93 (**33.3%**)	**10.2%** (-2.6%, 23.0%)	0.100

Clinical Response[§]	27/95 (**28.4%**)	39/93 (**41.9%**)	**13.5%** (-0.01%, 27.0%)	0.038

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
[#]High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
[‡] Clinical remission defined as PCDAI ≤ 10
[§] Clinical response defined as reduction in PCDAI of at least 15 points from baseline
Table above is modified from the Clinical Review. Source: Sponsor's response to IR July 31, 2014

In toto, I agree with the reviews and recommendation of the Clinical reviewer, Clinical Pharmacology reviewer and the CDTL, Dr. Rajpal, who recommends approval of this NDA based upon demonstrating efficacy of Humira for the treatment of moderate to severe Crohns disease in children.

8. Safety

The reader is referred to Dr. Dannis' 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 CD studies. There was no clear trend of higher incidence of AEs with increasing Humira dose or with Body Weight category seen in the pediatric CD studies.

No new safety signals were identified in review of the sBLA. Known events associated with the use of Humira appear to be adequately represented in current labeling.

9. Advisory Committee Meeting

No Advisory committee was held to review the issues in this application.

10. Pediatrics

a. Orphan Status and PREA Applicability: Orphan status for pediatric CD was granted October 19, 2006.[1] This was before the PREA PMC was issued (February 27, 2007) in the approval letter for the adult CD indication.[2] Section 50513(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 35513(k)) states that: "[u]nless the Secretary requires otherwise by regulation, this section [PREA] does not apply to any drug for an indication for which orphan designation has been granted under section 526 [of the Act]." Thus, a PREA PMC should not have been issued at the time of the

[1] http://www.accessdata fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=230306 (accessed August 31, 2014)
[2] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/125057s089Ltr.pdf (accessed August 31, 2014)

approval for adult CD. A letter was sent to the applicant on February 11, 2014 indicating that PREA did not apply to this application. Also, for this reason, the current sBLA was not presented to the Pediatric Research Committee (PeRC).

11. Other Relevant Regulatory Issues

1. OSI:
OSI concluded that the data generated by these sites are considered reliable in support of the application

12. Labeling

Specific revisions to the label are summarized in the CDTL Memorandum. 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):

 The Applicant's proposed wording (b) (4) was replaced with "inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate" to describe the population that was studied.

 Dosage and Administration (Section 2.4 of Label):
 The Applicant's proposal for a weight-tiered induction and maintenance dose (lower dose for patients < 40 kg; higher dose for patient's ≥ 40 kg) was accepted.

 The Applicant's proposal to recommend the high maintenance dose studied in the clinical trial (rather than the low maintenance dose studied in the clinical trial) was accepted.

(b) (4)

(b) (4)

Adverse Reactions (Section 6.1 of Label):

The Applicant's proposal to include the most common adverse reactions in the induction phase (injection site pain and injection site reaction) and the proportions of patients experiencing those adverse reactions was accepted.

The Applicant's proposal to include the proportion of patients experiencing an infection and to include specific infections (upper respiratory tract infection and nasopharyngitis) was accepted.

(b) (4)

The Applicant's proposal to include the proportion of patients experiencing a serious infection, and to include specific serious infections (viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis) was accepted.

The Applicant's proposal to include the proportion of patients experiencing allergic reactions and to provide a general description of these reactions as non-serious and primarily localized reactions was accepted. Clinical Studies (Section 14.6 of Label):

(b) (4)

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The proportions of patients receiving corticosteroids at baseline and receiving immunomodulators at baseline were included; also, the proportion of patients with loss of response or intolerance to a TNFα-antagonist was included.

Statements were added clarifying the following:

(b) (4)

Medication Guide:

What is HUMIRA? The wording below proposed by the Applicant was accepted as part of the bulleted list (of a number of Humira approved indicated populations) following

"To reduce the signs and symptoms of:" "moderate to severe Crohn's disease (CD) in children 6 years and older when other treatments have not worked well enough." It should be noted that this statement for pediatric CD parallels the previously existing wording here for adult CD ("moderate to severe Crohn's disease (CD) in adults when other treatments have not worked well enough.")

Instructions for Use:

In the first paragraph of each of the presentations of Humira (i.e., single-use pen, and single use prefilled syringe), the following was added: "It is also important to talk to your

doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time."

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review team functional areas have concluded that the efficacy supplement for Humira® (adalimumab) should be approved. This Signatory agrees with this recommendation for Approval.

13.2 Risk Benefit Assessment:

A well-defined, reliable, sensitive-to -treatment and globally recognized clinical outcome assessment (COA) tool that measures signs and symptoms in children with CD is needed to assess therapies for children with inflammatory bowel diseases. Qualification and use of PRO, endoscopy and/ or biomarkers as co-primary endpoints when needed might be helpful to expedite pediatric drug development. These issues remain to be clarified in the academic community.

The goals of clinical treatment for pediatric CD are to improve quality of life (reduction of diarrhea, bleeding, and abdominal pain as well as increase school attendance) and to prevent complications (strictures, abscess, growth failure, and colon cancer). It remains a topic for discussion whether these concepts can best be assessed for by a composite of PRO, ClinRO and biomarkers, or through the use of individually scored signs and symptoms. In either case, it would be very helpful for adequate measurement to maximize the endoscopic evaluations and encourage the patients to undergo baseline and follow up endoscopy in clinical trials. Currently, consideration of using co-primary endpoints of endoscopic improvement and a PRO that measures signs and symptoms if available might yield maximal information and ability to assess clinical benefit.

In principle, an age-appropriate set of PRO tools to be completed by an observer or the child, as appropriate, should be based on a firm understanding of disease definition according to clinically meaningful subgroups, and other aspects of the context of use to assure content validity. CD in children can present a complex spectrum of the manifestations: abdominal pain for most, diarrhea for some, bleeding for some, growth failure for 30%, EIM for some. With that in mind, a well-designed and adequate item generation process is essential. For this reason, adherence to the iterative process used in developing a PRO instrument for use in clinical trials is helpful and thus encouraged.

Mucosal healing has been increasingly recognized as an important outcome of medical treatment as it is associated with longer remission periods and reduced risk for surgeries and hospitalization, thus endoscopic or radiological based mucosal and histological examination may need to be considered as one outcome measurement. If or when a ClinRO tool of bowel inflammation is being developed, it would be helpful to explore the relationship between the proposed clinician-reported outcome of bowel inflammation and

patient-reported (or observer-reported) outcome measures (e.g., abdominal pain and stool frequency). Given the nature of this disease, it would be equally helpful to explore the relationship of intestinal destruction demonstrated from imaging studies to mucosal inflammation from endoscopy and histological measures in pediatric patients with Crohn's Disease. Meanwhile, we also acknowledge that there are many challenges to assessing mucosal healing in children with CD: reluctance to repeat endoscopies, inability to pass the scope to the disease site, need for standardization of endoscopic interpretation, etc. Many young children cannot undergo magnetic resonance enterography (MRE) because they are not able to drink the contrast, or stay still enough for optimal images. Additionally, understanding the importance of clinically relevant biomarkers, i.e. hematocrit and albumin, in constructing an endpoint model that reflects the clinical condition might yield clarity from a clinical and regulatory perspective. Exploration of additional models strengthening the basis for extrapolation from adult clinical trial data is needed moving forward in pediatric drug development for IBD therapies.

The collaboration of interested parties, including international regulatory bodies, pharmaceutical industry, academia, and patient groups, in the development of adequate outcome measures in pediatric CD is highly encouraged. To facilitate development of publicly available scientific tools to address unmet needs such as this, the FDA has initiated a drug development tool (DDT) qualification program that provides a framework for the development and regulatory acceptance of scientific tools, including clinical outcome assessments, intended for well-specified clinical trial contexts of use.

In regards to this application, the body of evidence for Humira® (adalimumab) supports the labeling for the indication reflecting a positive risk and benefit assessment for the proposed use of Humira® (adalimumab) for management of moderate to severe Crohns disease in children ages 6 and older.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:

There are no requirements for postmarketing evaluation.

Recommendation for other Postmarketing Requirements and Commitments

There are no Postmarketing Requirements or Commitments for this BLA.

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
09/23/2014
Deputy Director Summary Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: 125057/356

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Best, Jeanine
Brancazio, Matthew
Candauchacon, Maria
Chakder, Sushanta
Dannis, Marjorie
Dinatale, Miriam
Dowdy, Karen
Graham, Laurie
Ishihara, Richard
Kay, Ron
Lee, Jee Eun
Liebenhaut, Susan
Marin, Keith
Mehrotra, Nitin
Merchant, Lubna
Meyer, Joette
Mulberg, Andrew
Nguyen, Quynh Nhu
Nikhar, Bindi
Park, Jun
Sachs, Hari
Wang, Yow-Ming

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 19, 2014
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	BLA 125057/356
Applicant	Abbvie
Date of Submission	August 29, 2013
PDUFA Goal Date	September 29, 2014 (includes 3- month extension due to Major Amendment))
Proprietary Name / Established (USAN) names	Humira® / Adalimumab
Dosage forms / Strength	Current: ▪ single-use pen: 40 mg (0.8 mL) ▪ single-dose prefilled glass syringe: 20 mg (0.4 mL); 40 mg (0.8 mL) ▪ single use glass vial (for institutional use only): 40 mg (0.8 mL) Proposed: ▪ single-dose prefilled glass syringe: 10 mg (0.2 mL)
Proposed Indication	inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease
Recommended Action:	Approval

Table of Contents

1. Introduction

This application was submitted as an SE5 efficacy supplement (addition of pediatric use and dosing information) to the BLA (sBLA) for Humira (adalimumab) on August 29, 2013.

The proposed indication is "…for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4)

The Applicant proposed a weight-tiered induction and maintenance dose (lower dose for patients < 40 kg; higher dose for patients ≥ 40 kg), (b) (4)

The Applicant also proposed additions to the Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies sections.

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, plaque psoriasis, and ulcerative colitis. 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, followed two weeks later by a dose of 40 mg every other week.
- Crohn's disease and ulcerative colitis: 160 mg, followed two weeks later by a dose of 80 mg, followed two weeks later by a dose of 40 mg every other week.

2.2 Crohn's Disease

Crohn's disease (CD), also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. The disease is manifest as discontinuous transmural inflammatory changes that can occur anywhere in the GI tract but it

primarily involves small bowel or colon. Involved areas classically show noncaseating granulomas and fissuring. Complications include strictures, obstruction, malabsorption, malnutrition, and fistula formation. Growth retardation is a complication of concern in pediatric patients. There is an increased risk of malignancy with longstanding disease. Peak ages of diagnosis are the teens to twenties, but it can occur at any age.

2.3 Current Treatment Options for Crohn's Disease

Decisions about treatment of CD 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.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used, but unapproved, therapies are aminosalicylates, azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX). Use of any of the preceding has come to be considered part of "conventional therapy" for the disease.

For the proposed indicated population of pediatric patients 6 years of age and older with moderately to severely active Crohn's disease (b) (4) (b) (4) the only other approved treatment is Remicade (infliximab). Remicade was approved for a pediatric indication in CD in May 2006.[1]

2.4 Regulatory History

2.4.1 Regulatory History - Other TNFα-Antagonists for Pediatric CD

Remicade: Remicade (infliximab) was approved for adult CD in 1998.[2] Remicade was approved for pediatric CD in 2006.[2] In the pediatric CD study reported in the Remicade labeling, there was a single arm open label induction period (n=112) followed by a two-arm open-label maintenance period (103 patients were randomized to two different frequencies of maintenance dosing).[3] The study population was pediatric patients aged 6 to 17 years old with moderately to severely active CD and an inadequate response to conventional therapies.[3] The primary analysis was comparison of the clinical response rate (based on PCDAI) to the clinical response rate (based on CDAI) in adults in the "ACCENT I" study (one of the studies used for the adult CD approval).[4,5]

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/103772s5138ltr.pdf (accessed September 1, 2014)
[2] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/inflcen082498L.htm (accessed September 3, 2014)
[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf (accessed September 3, 2014)
[4] Supervisory Summary Review of sBLA103772/5138 Remicade for Pediatric Crohn's Disease (May 18, 2006).
[5] Clinical response based on PCDAI (in the pediatric CD Remicade study) was defined as a decrease in PCDAI of ≥ 15 points and a total PCDAI score of ≤ 30; clinical response based on CDAI (in the adult ACCENT I CD study) was defined as a decrease in CDAI of ≥ 70 points.

Cimzia: Cimzia (certolizumab) was approved for adult CD in 2008.[6] Cimzia is not currently approved for pediatric CD.

2.4.2 Regulatory History - Humira for Pediatric CD

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

Table 1. Pertinent Regulatory History of Humira for Pediatric CD (sBLA 125057/356)*

Date	Event
June 1, 2006	Pre-Phase 3 Meeting - pediatric development program
October 19, 2006	Orphan status granted for pediatric CD
February 27, 2007	**Humira approved for adult CD indication**
April 25, 2011	Teleconference
April 10, 2012	Pre-sBLA Meeting
August 29, 2013	**Current sBLA for pediatric CD submitted**

*IND 10425

Humira Approval for the Adult CD Indication (February 27, 2007): Humira was approved for adult CD with the following indication statement:

- "…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."
- "…for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab."

The approval for the adult CD indication was primarily based on results of: (a) a Phase 2/3 four-week induction trial (n=299); (b) a Phase 3 four-week induction trial (n=325); and (c) a Phase 3 56-week induction and maintenance trial (n=854). It should be noted that in one of the trials (the Phase 3 four-week induction trial), patients were required to have lost response to or be intolerant to infliximab. See Appendix 1 of this CDTL Review.

Orphan Status and PREA Applicability: Orphan status for pediatric CD was granted October 19, 2006.[7] This was before the PREA PMC was issued (February 27, 2007) in the approval letter for the adult CD indication.[8] Thus, a PREA PMC should not have been issued at the time of approval for adult CD. See Section 10 of this CDTL Review.

[6] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/125160s000ltr.pdf (accessed September 4, 2014)
[7] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=230306 (accessed August 31, 2014)
[8] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/125057s089Ltr.pdf (accessed August 31, 2014)

Key Comments Communicated to the Sponsor: Key comments communicated to the sponsor during the meetings and review of the IND submission included the following:

(1) Pre-Phase 3 Meeting - pediatric development program (June 1, 2006):

- Proposed Pediatric Indication: The Division did not agree with the Sponsor's initial proposal to (b) (4) (b) (4).
- Patients that Lost Response or are Intolerant to Remicade: The Division advised the sponsor to ensure an adequate representation of patients that have lost response to or are intolerant to Remicade (to fulfill PREA requirements for the adult CD approval).
- Placebo Control: The Division agreed that an adequate study may be performed without a placebo control group as the sponsor proposed. However, the Division stated the concern that the design will not be able to identify adequately the most appropriate dose and schedule.
- Induction of Remission Assessment: The Division noted that the Sponsor's proposal did not include an assessment for induction of remission. The Division suggested induction of remission be assessed at Week 8 or Week 4, noting that Week 4 would allow comparison to adult CD data. See Appendix 1.
- Collection of Both CDAI and PCDAI: The Sponsor was proposing to collect only PCDAI scores. The Division suggested collecting both CDAI and PCDAI at least in older patients or in a subset of older patients.
- (b) (4)

(2) (b) (4)

(3)

(b) (4)

- External Comparisons (to Adult Data): The Agency did not agree that the "external comparison" would necessarily provide sufficient evidence for judging the efficacy of adalimumab in this population; and further stated that these types of analyses were considered exploratory and have no statistical or inferential value.

See the Clinical Review by Marjorie Dannis for details of the Humira for Pediatric CD regulatory history.

2.5 Current Application

The application was received on August 29, 2013. It was classified as a ten-month submission with a PDUFA deadline of June 29, 2014. Because of a major amendment, the PDUFA date was extended to September 29, 2014.

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

(1) Clinical Review by Marjorie Dannis, dated August 29, 2014
(2) Statistics Review by Benjamin Vali, dated August 29, 2014
(3) Clinical Pharmacology Review by Jee Eun Lee and Jie Wang, dated August 21, 2014
(4) Pediatric and Maternal Health Staff (PMHS) Reviews:
    (a) Maternal Health Review by Miriam Dinatale, dated March 25, 2014
    (b) Pediatrics Review by Ethan Hausman, dated August 11, 2014
(5) Labeling Reviews:
    (a) Division of Medication Error Prevention and Analysis (DMEPA) Label, Labeling, and Packaging Review by Teresa McMillan dated May 16, 2014
    (b) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Karen Dowdy, dated August 14, 2014
    (c) Office of Prescription Drug Promotion (OPDP) Label Review by Meeta Patel, dated August 15, 2014
    (d) Division of Monoclonal Antibodies (DMA) Label Review by Jibril Abdus-Samad, dated September 15, 2014
(6) Office of Scientific Investigations (OSI) Clinical Inspection Summary by Susan Leibenhaut, dated May 12, 2014
(7) Quality Review by Jun Park, dated June 2, 2014
(8) Quality Microbiology Review by Reyes Candau-Chacon, dated May 30, 2014
(9) CDRH Office of Compliance Consult Review by Viky Verna, dated August 19, 2014
(10) CDRH Human Factors Premarket Evaluation Team (HFPMET) Review, dated September 2, 2014

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

The reader is also referred to the following reviews from the Humira for adult CD efficacy supplement approved February 27, 2007:

- Clinical Team Leader Memo by John Hyde, dated February 27, 2007
- Clinical Review by Li-Ching Liang, dated February 27, 2007
- Clinical Pharmacology Review by Tien-Mien Chen, dated February 27, 2007

3. CMC

The reader is referred to the Quality Review by Jun Park for full information.

The following is summarized from the Quality Review.

Current: Humira is currently licensed at 50 mg/mL as either:

- 40 mg/0.8 mL prefilled syringe
- 20 mg/0.4 mL prefilled syringe
- 20 mg/0.4 mL prefilled pen
- 40 mg/0.8 mL glass vial (institutional use only)

Proposed: The Applicant is proposing the following:

- **10 mg/0.2mL PFS presentation**

Clinical Studies: In the clinical studies (M06-806 and M06-807), Humira was administered as follows:

- Study M06-806:
  - Induction: glass vials at 50 mg/mL
  - Maintenance: glass vials at either 50 mg/mL or 25 mg/mL.
- Study M07-807:
  - 20 and 40 mg doses: prefilled syringe at 50 mg/mL
  - 10 mg dose: glass vial at 50 mg/mL

Data to Support the 10 mg/0.2 PFS: The formulation and container closure of the drug product in the proposed **10 mg/0.2mL PFS presentation** is identical to the approved Humira presentations. A description of the manufacturing process for the 10 mg/0.2 mL PFS in the submission included testing results for the characterization/comparability, process validation, batch release, and stability. It should be noted that there does not appear to be any clinical experience with the 10 mg PFS. The sponsor is relying upon clinical data for a 10 mg maintenance dose that is based on either the 50 mg/mL vial or a 25 mg/mL vial.

Data to Support 25 mg/mL, 0.8 mL in Vial: As AbbVie used adalimumab 25 mg/mL, 0.8 mL in vial for the M06-806 pivotal clinical study, a description of the manufacturing process for the adalimumab 25 mg/mL, 0.8 mL in vial was provided along with testing results for the characterization, comparability, batch release, and stability.

Anti-Drug Antibody Assay: There was also updated information provided for the anti-drug antibody (ADA) assay. Specifically, the original ADA assay was validated at Abbott Laboratories in Ludwigshafen Germany. The assay was revalidated at the same site with

slight modifications to [redacted] (b) (4). This re-validated assay was transferred to [redacted] (b) (4). The current submission contains the partial validation of the assay at [redacted] (b) (4)

Confirmatory ADA Assay: In addition, the sponsor made a change in the confirmatory ADA assay which involved [redacted] (b) (4). The partial revalidation report for the confirmatory assay was also provided in this submission.

Conclusion: The Quality Reviewer found these data to be acceptable, and recommended approval from a CMC persepective.

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology/Biopharmaceutics

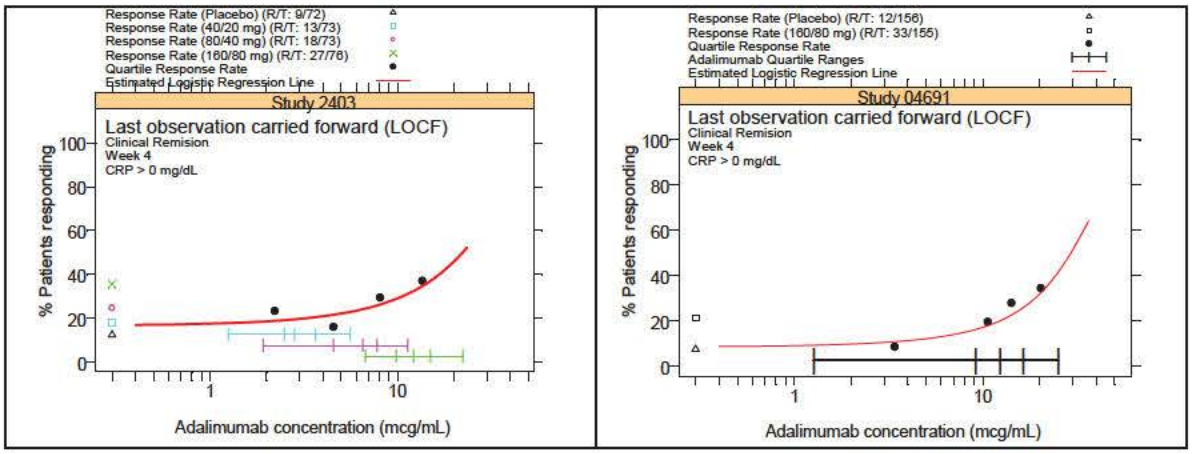
The reader is referred to the Clinical Pharmacology Review by Jee Eun Lee and Jie Wang for complete information.

5.1 Summary of Adult CD Data

Induction:

The following was noted in the Clinical Pharmacology Review of the sBLA for adult CD:[9]

The probability of clinical remission (defined as CDAI < 150) in the induction studies is clearly dependent upon the adalimumab concentration.

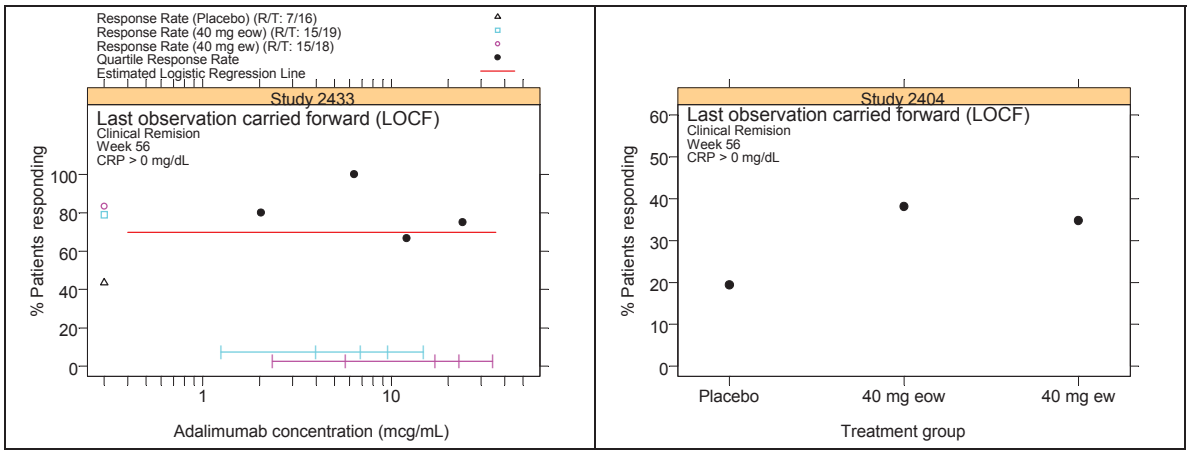


[9] Clinical Pharmacology Review by Tien-Mien Chen (Humira for Adult CD), February 27, 2007

Maintenance:

The following was noted in the Clinical Pharmacology Review of the sBLA for adult CD:[9]

There is no clear evidence of exposure-response for clinical remission in the maintenance studies (see figures below). However, the percentage patients responding in the active treatment groups in maintenance studies 2433 and 2404 are clearly separated from the placebo group. The efficacy is comparable between every other week (eow) and every week (ew) dosing.



5.2 Induction Dosing Regimen - Pediatric CD

Induction Dosing Regimen Studied/Proposed: The induction dosing regimen studied was: 160 mg on Day 1 and 80 mg on Day 15 (in patients with body weight ≥ 40 kg); and 80 mg on Day 1 and 40 mg on Day 15 (in patients with body weight < 40 kg). This is the induction dosing regimen the Applicant proposed for labeling.

Exposure-Response Relationship: The Clinical Pharmacology Reviewers noted that there was no exposure-response relationship observed during the induction phase of Study M06-806. The Clinical Pharmacology Reviewers also noted that rates of clinical remission at Week 4 are comparable between the two groups of patients (< 40 kg and ≥ 40 kg). See the figure and table below.

Figure 1. Exposure-response relationship between adalimumab concentration at Week 4 and clinical remission at Week4 *(Reviewer's analysis)*

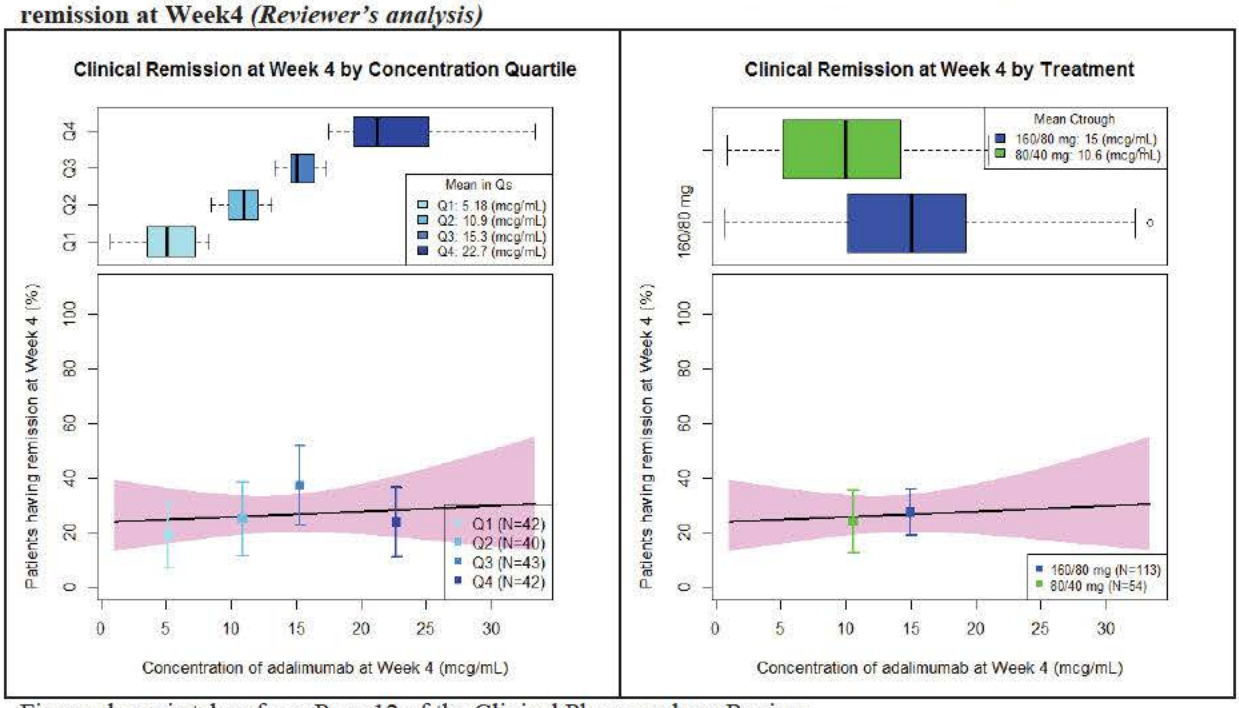


Figure above is taken from Page 12 of the Clinical Pharmacology Review.

Comparison to Adult Data: The Clinical Pharmacology Reviewers noted that trough concentrations and the proportion of patients in clinical remission at Week 4 were comparable with those in adults following the 160/80 mg dosing regimen. See the table below.

Table 2. Summary of Concentration of Adalimumab and Clinical Remission at Week 4 by Treatment Group and Population

Population	Subgroup	Dose	Ctrough (mcg/mL, Mean ± SD)	Clinical Remission at Week 4
Pediatrics	**< 40 kg (N=54)**	80/40 mg	**10.57** ± 6.00	13/54 (**24.1%** [12.7, 35.5])
	≥ 40 kg (N=113)	160/80 mg	**14.97** ± 6.94	31/113 (**27.4%** [19.2, 35.7])
Adults (M02-403)	**N=76**	160/80 mg	**12.61** ± 5.25	27/76 (**35.5%**)
Adults (M04-691)	**N=159**	160/80 mg	**12.63** ± 6.04	34/159 (**21.4%**)

(Reviewer's analysis for pediatrics. Source for adult data: M02-403 CSR Table 20, M02-403 PK Report page 4, M02-691 Table 16, M02-691 PK Report page 5)
Table above is taken from Page 13 of the Clinical Pharmacology Review.

Conclusion: The Clinical Pharmacology Reviewers concluded that the proposed induction dosing regimen is acceptable.

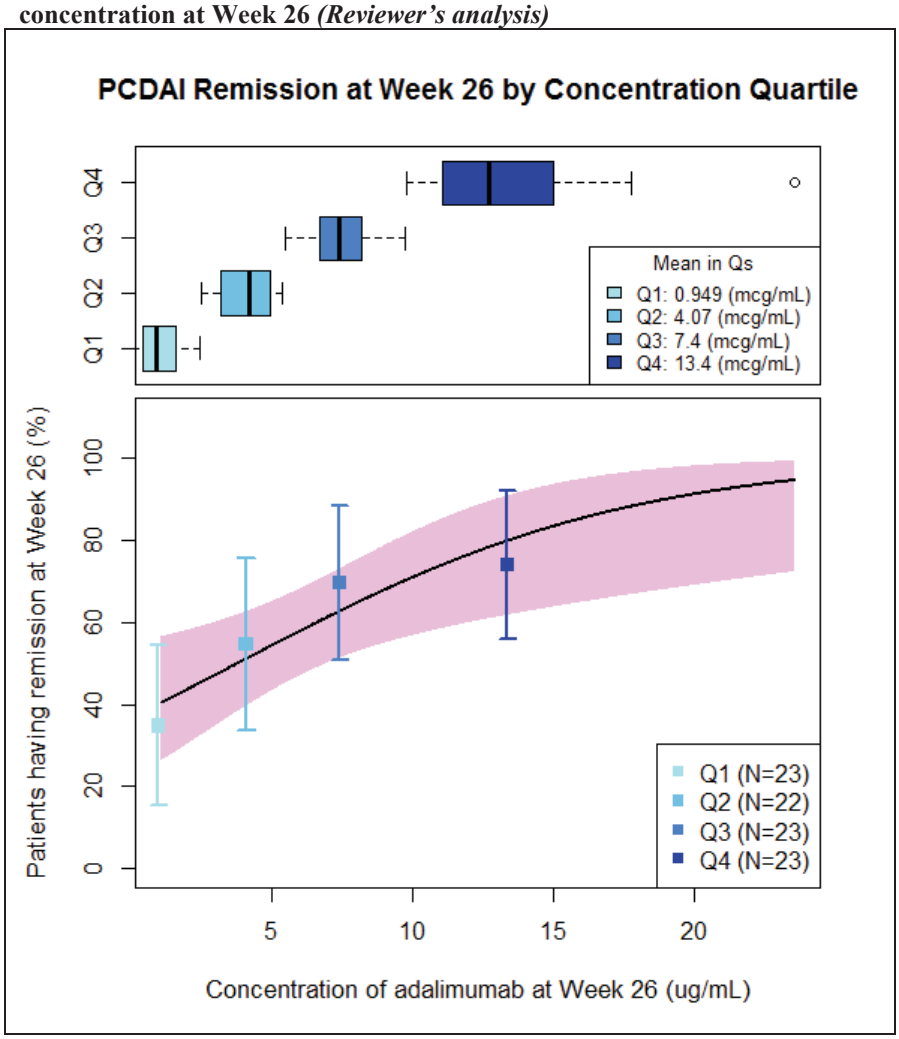
5.3 Maintenance Dosing Regimen - Pediatric CD

Maintenance Dosing Regimen Studied: Two maintenance dosing regimens were studied: (a) Low Dose (20 mg EOW in patients with body weight ≥ 40 kg and 10 mg EOW in patients

with body weight < 40 kg); and (b) High Dose (40 mg EOW in patients with body weight ≥ 40 kg and 20 mg EOW in patients with body weight < 40 kg).

Exposure-Response Relationship: The Clinical Pharmacology Reviewers noted that a statistically significant (p=0.006) exposure-response relationship between PCDAI clinical remission at Week 26 and observed trough concentration of adalimumab at Week 26 provides supportive evidence of effectiveness for adalimumab in the treatment of CD in pediatric patients (see figure below).

Figure 2. Logistic regression for PCDAI clinical remission at Week 26 by quartile of adalimumab trough concentration at Week 26 *(Reviewer's analysis)*



The figure above is taken from Page 10 of the Clinical Pharmacology Review.

Exposure-Response Relationship (By Treatment): The Clinical Pharmacology Reviewers noted that the exposure-response relationship between trough concentrations at Week 26 and clinical remission (based on unadjusted PCDAI) at Week 26 showed that the High Dose group achieved greater clinical remission than the Low Dose group. See the figure below.

Figure 3. PCDAI clinical remission at Week 26 (N=133, subjects who stayed with the original therapy until Week 26) *(Reviewer's analysis)*

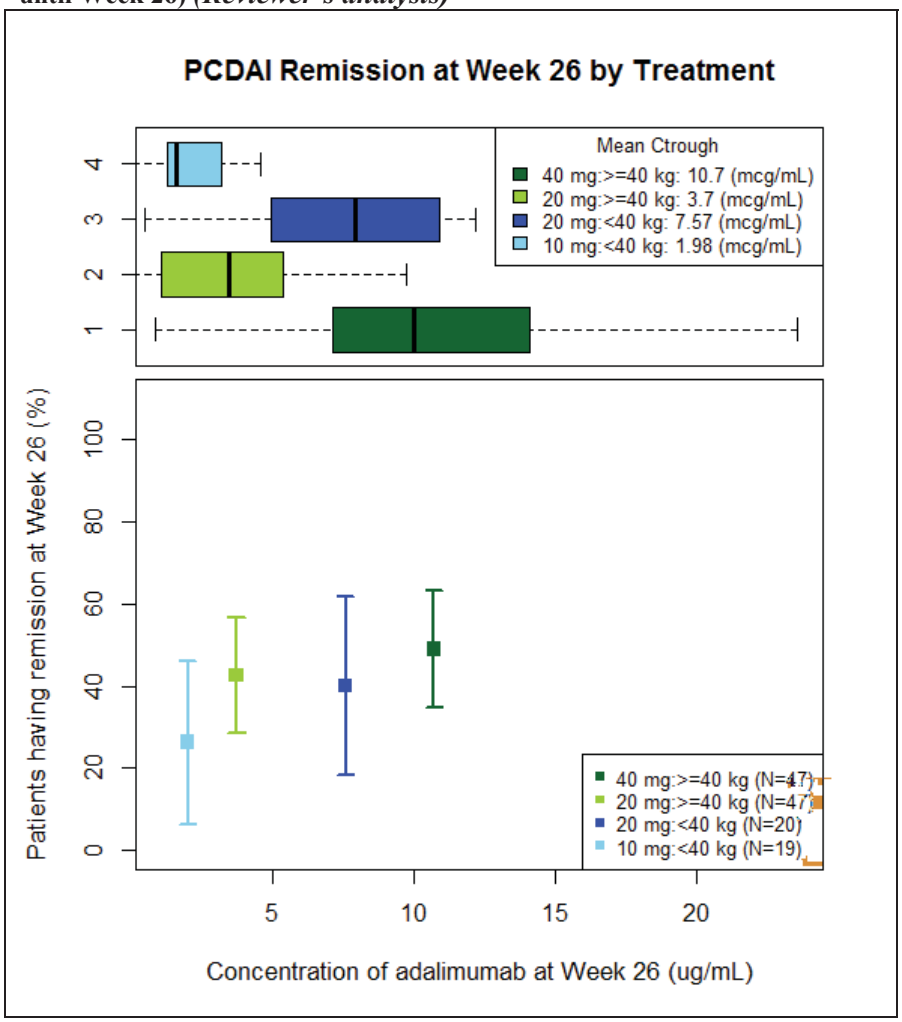


Figure above taken from Page 13 of the Clinical Pharmacology Review.

The Clinical Pharmacology Reviewers also noted that concentrations following the Low Dose are lower than concentrations observed with 40 mg EOW in adults. See Section 5.6 of this CDTL Review.

Dose-Response Relationship: The Clinical Pharmacology Reviewers noted that the above is consistent with the dose-response observed for clinical remission at week 26. The Clinical Pharmacology Reviewers also noted that there was a trend in dose response for the secondary endpoints (clinical remission at Week 52, clinical response at Week 26, and clinical response at Week 52). See Section 7.4.3 of this CDTL Review. The Clinical Pharmacology Reviewers commented that when clinical remission was evaluated over time, the high dose consistently showed a numerically higher proportion of patients in clinical remission than the low dose during the maintenance phase. See the figure below.

Figure 4. Odds ratio for High Dose relative to Low Dose for Clinical Remission over time *(Reviewer's analysis)*

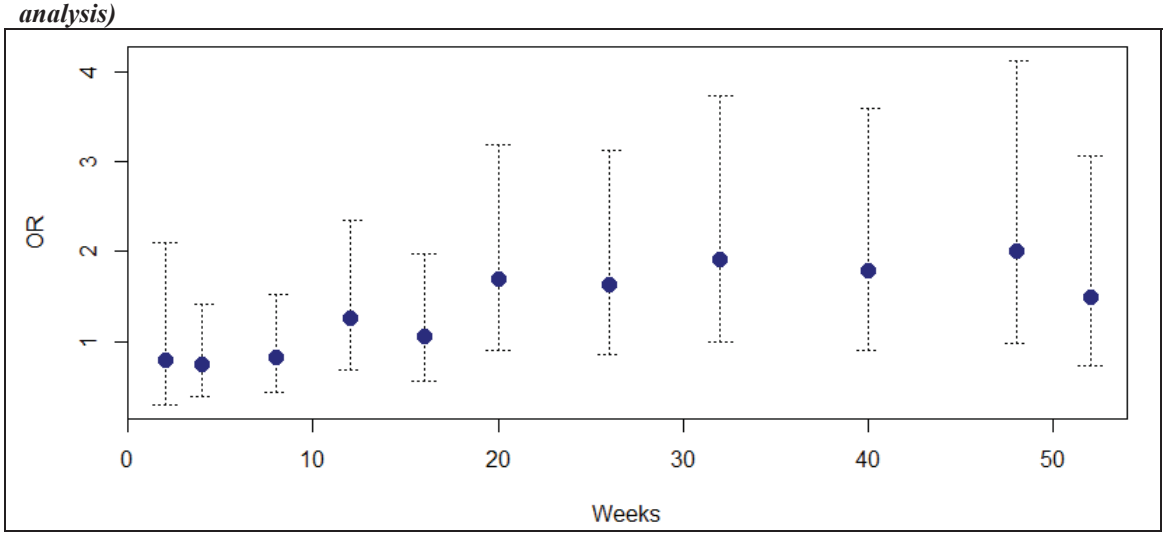


Figure above is taken from Page 16 of the Clinical Pharmacology Review.

Proportion of Patients that Dose-Escalated (from EOW to EW): The Clinical Pharmacology Reviewers noted that a higher proportion of patients in the Low Dose group (51%) dose-escalated compared to the High Dose group (38%) due to a disease flare or inadequate response.

Conclusion: The Clinical Pharmacology Reviewers concluded that the High Dose should be the recommended maintenance dosing regimen.

(b) (4)

Table 3. Clinical Remission and Clinical Response at Week 52 by Dose-Escalation (EOW to EW) and Week 4 Response Status

		Low Dose (20 mg or 10 mg)	High Dose (40 mg or 20 mg)
Clinical remission at Week 52			
Overall		4/48 (8.3%)	5/35 (14.3%)
	Patients who were responder at Week 4	3/41 (7.3%)	5/26 (19.2%)
	Patients who were non-responder at Week 4	1/7 (14.3%)	0/9
Clinical Response at Week 52			
Overall		13/48 (27.1%)	13/35 (37.1%)
	Patients who were responder at Week 4	12/41 (29.3%)	12/26 (46.2%)
	Patients who were non-responder at Week 4	1/7 (14.3%)	1/9 (11.1%)

(Reviewer's analysis: Last observation carried forward (LOCF) method was used for this analysis)
The table above is taken from the Clinical Pharmacology Review (page 23).

(b) (4)

5.6 Pharmacokinetics

The Clinical Pharmacology Reviewers noted the following pharmacokinetics results:

Subjects weighing ≥ 40 kg: The mean serum adalimumab concentrations were as follows:
- Week 4: 15.7 mcg/mL (160 mg at Week 0 and 80 mg at Week 2)
- Week 26: 11.1 mcg/mL (40 mg EOW group); 3.9 mcg/mL (20 mg EOW group)
- Week 52: 10.5 mcg/mL (40 mg EOW group); 3.8 mcg/mL (20 mg EOW group)

Subjects weighing < 40 kg: The mean serum adalimumab concentrations were as follows:
- Week 4: 10.6 mcg/mL (80 mg at Week 0 and 40 mg at Week 2)
- Week 26: 8.3 mcg/mL (20 mg EOW) and 2.7 mcg/mL (10 mg EOW)
- Week 52: 6.9 mcg/mL (20 mg EOW) and 2.6 mcg/mL (10 mg EOW)

The table below shows a summary of serum adalimumab trough concentrations in pediatric subjects with CD who remained on their original randomized therapy; adult CD data are included for reference.

Table 4. Summary of Serum adalimumab Trough Concentrations in Pediatric Subject with CD Who Remained on Their Original Randomized Therapy

Treatment groups	Dose (body weight, n)	Adalimumab concentrations (Mean ± SD, mcg/mL)				
		Week 2	Week 4	Week 16	Week 26	Week 52
High Dose (40/20 mg EOW)	Combined (N=53)	16.2±6.07	15.5±6.74	10.3±4.80	10.4±4.26	9.48±5.61
	40 mg EOW (≥ 40 kg, N=36)	16.4±5.61	16.2±6.54	11.3±4.82	11.1±4.50	10.5±5.99
	20 mg EOW (< 40 kg, N=17)	15.7±7.09	14.1±7.13	7.73±3.83	8.32±2.62	6.89±3.55
Low Dose (20/10 mg, EOW)	Combined (n=45)	14.6±4.77	12.4±6.17	3.98±2.38	3.63±2.50	3.51±2.21
	20 mg EOW (≥ 40 kg, N=34)	15.1±4.89	12.8±6.47	4.25±2.52	3.90±2.69	3.80±2.24
	10 mg EOW (< 40 kg, N=11)	13.1±4.22	11.2±5.27	3.07±1.63	2.70±1.48	2.60±2.00
		Week 4	Week 4		Week 24	Week 56
Adult data as reference*	160 mg/80 mg at Weeks 0/2	12.34 ± 3.68	12.61 ± 5.25	NA	NA	NA
	40 mg EOW	NA	NA	NA	8.20 ± 4.69	10.92 ± 6.57

(Data source: Table 4 and Table 5, Adalimumab M06-806 Pharmacokinetic Report R&D/10/97; M02-403 for induction phase and M02-433 for maintenance phase)

The table above is taken from the Clinical Pharmacology Review Page 26.

Conclusion: The Clinical Pharmacology Reviewers commented that the PK results indicated that the pediatric subjects receiving the Low Dose (20 mg EOW for ≥40 kg and 10 mg EOW for <40 kg) had generally lower steady state exposure than that observed in adult subjects receiving the approved dose of 40 mg EOW.

5.7 Immunogenicity

The Clinical Pharmacology Reviewers noted the following immunogenicity results:

- Incidence of Anti-Drug Antibody Development: In Study M06-806, 182 subjects had the immunogenicity samples collected according planned schedule in the protocol. Of these 182 subjects, 58 subjects had at least one sample tested for anti-drug antibody (ADA). A total of 6 subjects among the 58 subjects with samples tested were determined as ADA positive; therefore, the incidence of ADA development was 10.3% (6/58).

- Incidence of Anti-Drug Antibody Development - Alternate Calculation: The applicant also provided an alternate calculation of ADA formation rate based on the 182 subjects who received adalimumab treatment, which resulted in the ADA development rate of 3.3% (6/182). The remaining 124 subjects were not tested for ADA because all their immunogenicity samples had adalimumab concentration ≥ 2 mcg/mL which prevents the detection of ADA. Due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL.

- Effect of ADA on PK: The PK results indicated that ADA formation was associated with decreased adalimumab exposure in pediatric subjects with CD. The majority of PK

samples in ADA positive subjects had serum adalimumab concentrations declined to below the lower limit of quantitation (LLOQ, 31.25 ng/mL) of the PK assay.

-
- Effect of ADA on the Efficacy or Safety of Adalimumab: The number of subjects who had ADA samples tested and confirmed to have developed ADA was too small to determine the effect of ADA on the efficacy or safety of adalimumab in pediatric subjects with CD.

The Clinical Pharmacology Reviewers agreed with the Applicant's proposed labeling in the "Immunogenicity" sub-section of Section 6.1 Clinical Trials Experience"

Immunogenicity

"In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was (b) (4)%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 µg/mL. Among the patients whose serum adalimumab levels were < 2 µg/mL (approximately 32% of total patients studied), the immunogenicity rate was (b) (4)%."

5.8 Final Recommendation

An Approval Action is the recommendation by the Clinical Pharmacology discipline.

(b) (4)

The Clinical Pharmacology Reviewers also recommend the following: (1) The Applicant's proposed induction dosing regimen should be accepted (see Section 5.2 of this CDTL Review); (2) The High Dose studied in the maintenance phase should be the recommended maintenance dosing regimen (see Section 5.3 of this CDTL Review); and (3) (b) (4)

See also Section 7.5 Final Recommendation in the Clinical/Statistical - Efficacy section)

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 the Clinical Review by Marjorie Dannis, and the Statistics Review by Benjamin Vali for complete information.

7.1 Background - Extrapolation of Efficacy

Extrapolation of efficacy in pediatrics is discussed in the Code of Federal Regulations (see 21 21 CFR 601.27) as follows (emphasis added):

> "Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be **extrapolated** from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."

The pediatric extrapolation decision tree (see figure below) presents the assumptions and requirements for using extrapolation to support efficacy in pediatric patients.[10] This algorithm represents a decision schema that helps to identify studies that are needed to support pediatric labeling when extrapolation is considered appropriate.[11]

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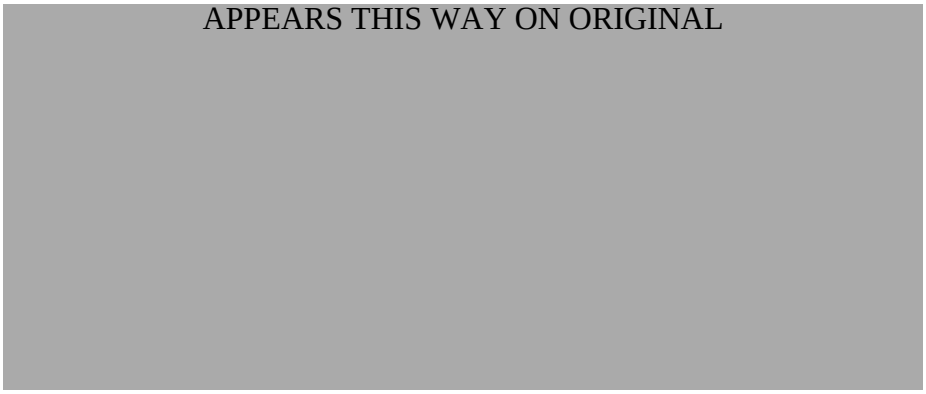
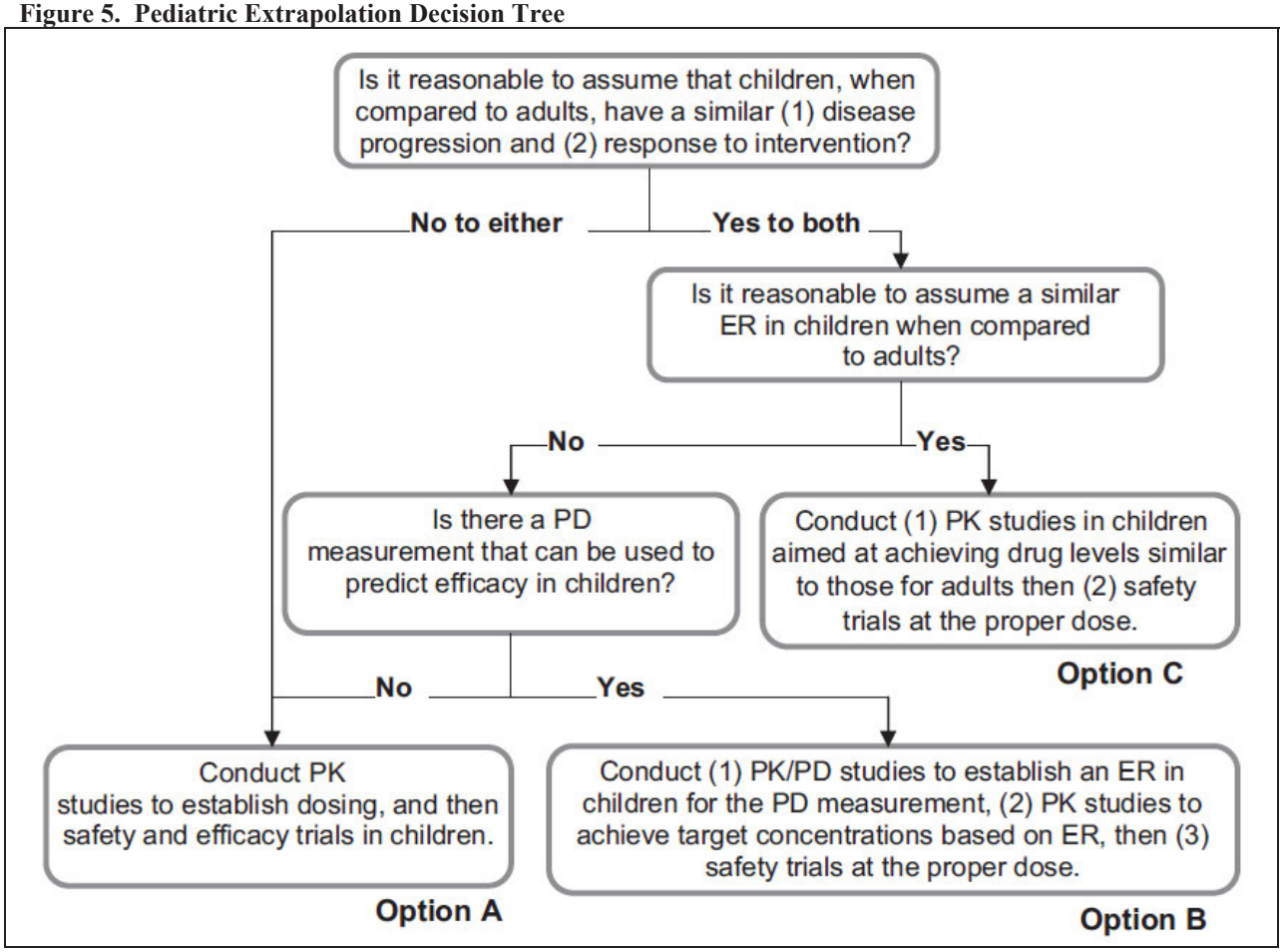


[10] Dunne J et al., "Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs", PEDIATRICS Volume 128, Number 5, November 2011

[11] This algorithm was presented and discussed at the Gastrointestinal Drugs Advisory Committee (July 21, 2011) for Remicade for Pediatric UC in the context of pediatric study requirements for extrapolation of efficacy from adult data. Meeting Materials are available at: http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm235600 htm (accessed September 3, 2014)

Figure 5. Pediatric Extrapolation Decision Tree



The figure above is taken from Dunne J et al., "Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs", PEDIATRICS Volume 128, Number 5, November 2011

If the basic assumption in the first decision point ("Is it reasonable to assume that children when compared to adults have a similar disease progression and response to intervention") cannot be made, adequate and well-controlled pediatric trials would be required (see Option A in the diagram above). It should be noted that the only other approved TNFα-antagonist for pediatric CD (Remicade) did not rely on adequate and well-controlled pediatric trials as the basis of approval for the pediatric CD indication (see Section 2.4.1 of this CDTL Review).

There is uncertainty about the next decision point ("Is it reasonable to assume a similar exposure-response (ER) in children when compared to adults?). Thus, PK studies alone (Option C in the diagram above) (full extrapolation) would not be appropriate

For the next decision point ("Is there a pharmacodynamic (PD) measurement that can predict efficacy in children?), the answer is "Yes" because in the case of pediatric CD, there are clinical efficacy endpoints (such as the CDAI and PCDAI) that can be used as pharmacodynamic (PD) markers to predict efficacy. Thus, Option B in the diagram above (partial extrapolation), reliance on both PK data and PD data (which in this case is clinical response data), is the appropriate approach.

7.2 Proposed Indication

The proposed indication for pediatric CD is shown in the table below along with the proposed indication for adult CD (emphasis added):

Table 5. Humira Adult CD Indication and Proposed Pediatric CD Indication

Adult CD Indication	Proposed Pediatric CD Indication
• "…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**. • "…for **reducing signs and symptoms** and **inducing clinical remission** in these patients **if they have also lost response to or are intolerant to infliximab**."	• "…for **reducing signs and symptoms** and **inducing and maintaining clinical remission** in **pediatric patients 6 years of age and older** with moderately to severely active Crohn's disease who (b) (4) (b) (4)

See Section 12 of this CDTL Review for a discussion of revisions to the label.

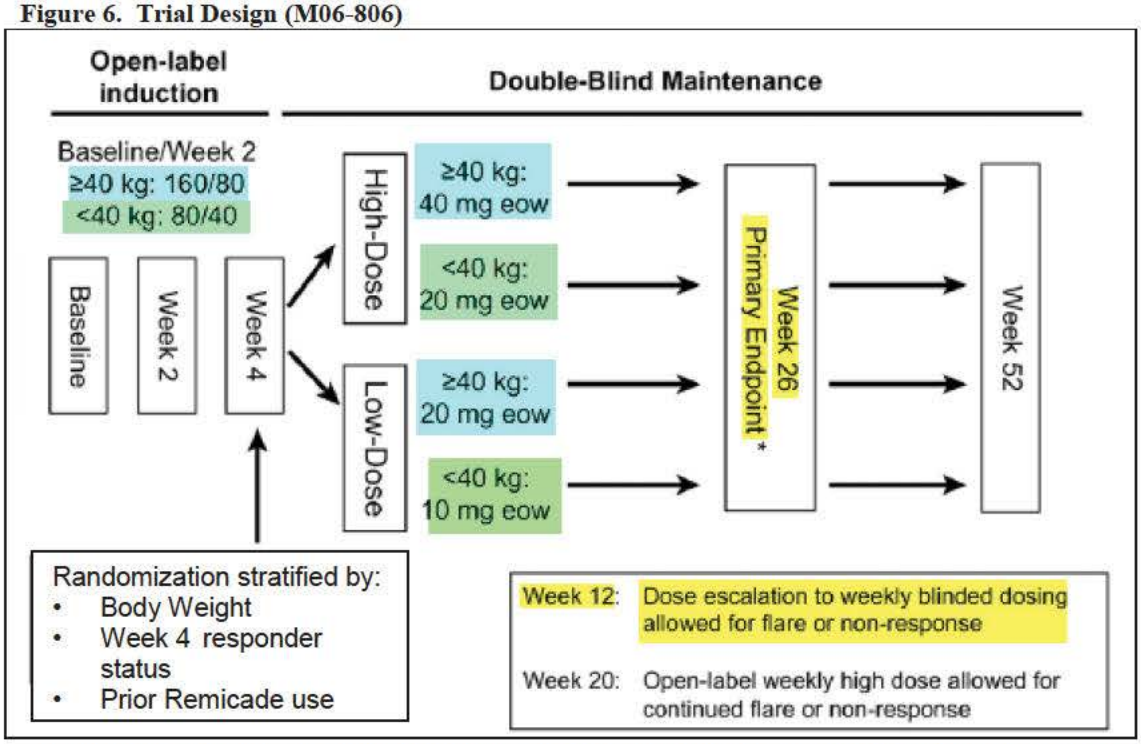
7.3 Design of the Pediatric CD Trial (M06-806)

7.3.1 Design:

The diagram below provides a simplified overview of the trial design. More detailed diagrams can be found in the Clinical and Statistical reviews.

Patients received open-label induction therapy at a dose based on their body weight (≥40 kg and <40 kg). Patients weighing ≥ 40 kg received 160 mg (at Week 0) and 80 mg (at Week 2). Patients weighing < 40 kg received 80 mg (at Week 0) and 40 mg (at Week 2). At Week 4, patients within each body weight category (≥40 kg and <40 kg) were randomized 1:1 to one of two maintenance dose regimens (high dose and low dose). The high dose was 40 mg every other week for patients weighing ≥ 40 kg and 20 mg every other week for patients weighing < 40 kg. The low dose was 20 mg every other week for patients weighing ≥ 40 kg and 10 mg every other week for patients weighing < 40 kg.

Figure 6. Trial Design (M06-806)



*The primary endpoint was Clinical Remission at Week 26 (clinical remission defined based on PCDAI)
The diagram above is modified from: Hyams JS, Griffiths A, Markowitz J, et al., "Safety and Efficacy of Adalimumab for Moderate to Severe Crohn's Disease in Children", GASTROENTEROLOGY 2012;143:365–374.

7.3.2 Key Entry Criteria:

Key entry criteria are shown below.

1. Ages 6-17 years old
2. CD diagnosis at least 12 weeks confirmed by endoscopy or radiologic evaluation.
3. Moderately to severely active CD (PCDAI > 30) despite concurrent steroids and/or immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) or inadequate response/intolerance to steroids and/or immunomodulators in the past 2 years (based on investigator opinion)
4. Patients who had previously received Remicade were allowed to enroll if they had previously had loss of response or intolerance to Remicade (see criteria defining loss of response or intolerance to Remicade in the Clinical Review).

For additional details of entry criteria, see the Clinical Review.

7.3.3 Randomization and Stratification:

Randomization: At Week 4, patients were randomized 1:1 to High Dose or Low Dose.

Stratification: Patients were stratified by:

- Body weight
- Week 4 responder status
- Prior Remicade use

7.3.4 Concomitant Medications Allowed:

Concomitant stable dosages of corticosteroids (prednisone dosage ≤40 mg/day or equivalent) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted throughout the study.

7.3.5 Dose-Escalation:

At Week 12, patients who experienced a disease flare (increase in PCDAI of ≥ 15 from Week 4 and absolute PCDAI > 30) or who were non-responders (did not achieve a decrease in the PCDAI of ≥ 15 from baseline for 2 consecutive visits at least 2 weeks apart) were allowed to dose-escalate (i.e., switch from blinded every other week dosing to blinded every week dosing); patients who dose-escalated were considered treatment failures.

At Week 20, dose escalation to open label weekly high dose was allowed for continued disease flare or non-response.

7.3.6 Endpoints:

Primary and Secondary Endpoints:

The primary and secondary endpoints are shown in the table below.

Table 6. Primary and Secondary Endpoints (Study M06-806)

Endpoint	Definition	Comparison
Primary:	**Clinical Remission* at Week 26**	**High Dose vs. Low Dose**; and ***External Comparison (M02-404)***
1st Ranked Secondary:	Clinical Remission* at Week 52	High Dose vs. Low Dose
2nd Ranked Secondary:	Clinical Response# at Week 26	High Dose vs. Low Dose
3rd Ranked Secondary:	Clinical Response# at Week 52	High Dose vs. Low Dose
4th Ranked Secondary:	Clinical Remission* at Week 26 (Subgroup of Responders# at Week 4)	*External Comparison (M02-404)*
5th Ranked Secondary:	Clinical Remission* at Week 4	*External Comparison (M02-404)*

*Clinical Remission: PCDAI ≤ 10; #Clinical Response: PCDAI decrease ≥ 15 from Baseline

Additional secondary endpoints are described in the Clinical Review.

External Comparisons using "Adjusted PCDAI Remission":

In addition to the comparison between the High Dose and Low Dose groups within Study M06-806, the analysis of the primary endpoint included an external comparison (to adult data from Study M02-404). The analyses of the fourth-ranked and fifth-ranked secondary endpoints were each based on an external comparison (to adult data from Study M02-404). In order to conduct these analyses, the Applicant used a conversion factor based on patients that were ≥ 13 years of age (who had both CDAI and PCDAI) to adjust PCDAI-based remission rates (from this study) in order to compare to CDAI-based remission rates (in the adult study M02-404). The Statistics Review provides details of the calculation of "adjusted PCDAI remission". In short, a Conversion Factor (CF) was calculated (based on data from ≥ 13 years old patients in Study M06-806) as follows: CF = (percentage of patients in CDAI-based Clinical Remission at Week 26) ÷ (percentage of patients in PCDAI-based Clinical Remission at Week 26). Then, this CF was applied to all patients in Study M06-806 to calculate "adjusted PCDAI Remission" rates.

Discussion of External Comparisons using "Adjusted PCDAI Remission":

The Statistical Reviewer commented that "…external endpoint analyses were all exploratory in nature (b) (4) (b) (4) The Clinical Reviewer also commented that these "external comparisons" were considered exploratory and cited the Pre-sBLA Meeting in which this point was communicated to the sponsor (see also Section 2.4.2 of this CDTL Review).

This Reviewer agrees with the Statistical Reviewer and Clinical Reviewer that these analyses should be considered exploratory only. However, this Reviewer believes it is important to present the external data from the adult study alongside the results of the pediatric study so a descriptive comparison can be made.

In addition, it is worth reviewing the key differences between the CDAI and PCDAI (shown below)(see also Appendix 2).

- PCDAI includes assessments of height/growth, ESR, albumin, and perirectal disease whereas CDAI does not.
- CDAI includes an assessment of use of opiates for diarrhea whereas PCDAI does not.

See the CDAI Scoring System in Appendix 3, and the PCDAI Scoring System in Appendix 4.

In the review of the Remicade for Pediatric CD sBLA, the Clinical Team Leader Memo stated (based on data from a Phase 2 study of Remicade for Pediatric CD that included remission rates based on both scoring systems) that "…the PCDAI criteria for remission appeared to be a 'higher bar' compared to the CDAI criteria."[12] In that Memo, the Clinical Team Leader further concluded: "…it appears reasonable to interpret the results of the REACH Study as showing that the response rates for Remicade in pediatric Crohn's disease are at least as high as the rates for Remicade in adult Crohn's disease."

[12] Clinical Team Leader Memo (Remicade for Pediatric Crohn's Disease) by John Hyde, Ph.D., M.D.

Data from the current efficacy supplement (comparing remission rates based on CDAI to remission rates based on PCDAI) (albeit limited to subjects 13 years old and greater) also suggest that PCDAI criteria for remission is a "higher bar" compared to the CDAI criteria for remission. The conversion factor (ratio of the number of subjects achieving CDAI remission criteria to the number of subjects achieving PCDAI remission criteria) is greater than one (see Appendix 5).

This CDTL Review presents external data from Study M02-404 and the Applicant's analyses as follows:

- For the purpose of descriptive comparison only, the adult data (from Study M02-404) (for CDAI remission) is presented alongside the data from this study (for un-adjusted PCDAI remission) for the primary endpoint, fourth-ranked secondary endpoint, and fifth-ranked secondary endpoint. See Section 7.4.3.
- As the Applicant's analyses of the comparison using "adjusted PCDAI remission" data from this study to external data (from Study M02-404) (using CDAI remission) (for the primary endpoint, fourth-ranked secondary endpoint, and fifth-ranked secondary endpoint) are considered exploratory only, the results are not included in the main section of this CDTL Review, but are included for completeness in Appendix 6

7.4 Results

7.4.1 Demographics and Baseline Characteristics:

Demographic Characteristics: Demographic characteristics were balanced across dose groups. The majority of subjects were male (56%), white (88%), and ≥ 13 years old (65%). The median age was 14 years.

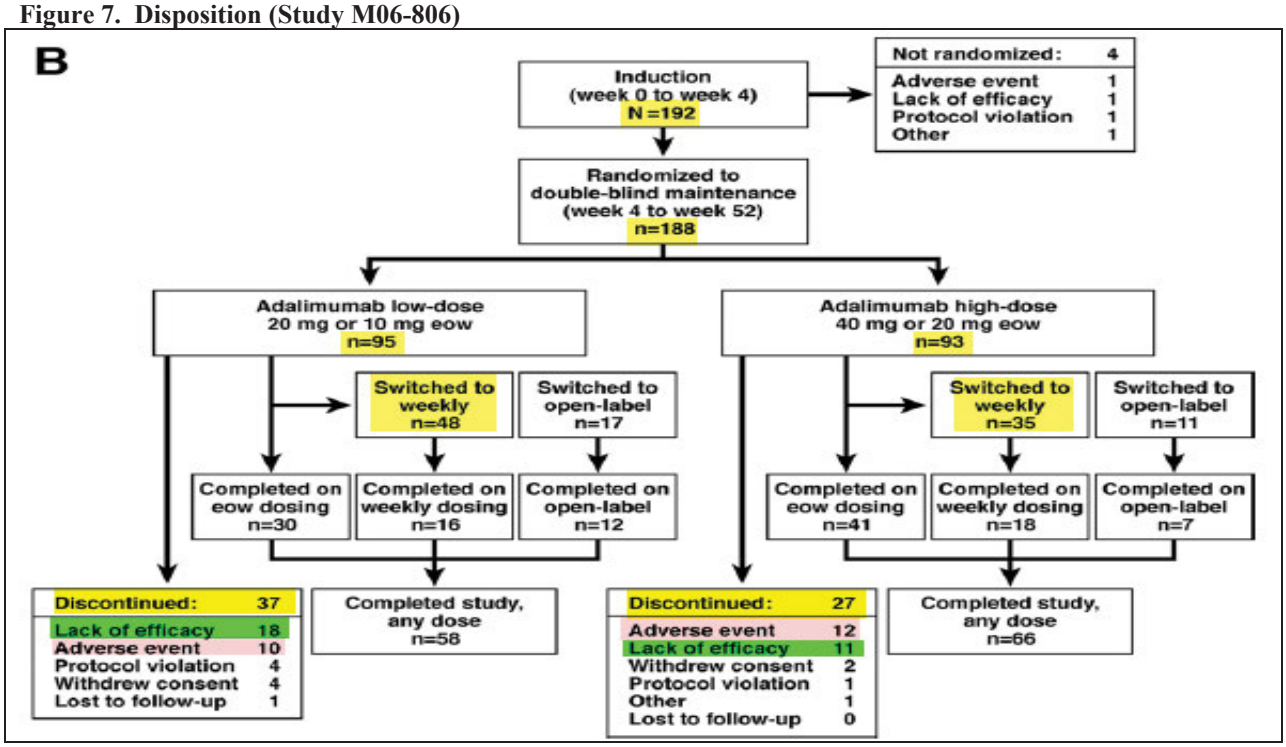
Baseline Characteristics: Baseline characteristics were generally balanced across dose groups; however, the Clinical Reviewer commented that the High Dose group appeared to have a higher CDAI score[13] at Baseline than the Low Dose group (mean CDAI 279 vs. 243). The median baseline PCDAI score was 40. At baseline, 38% of patients were receiving corticosteroids, and 62% of patients were receiving an immunomodulator. Forty-four percent (44%) of patients had previously lost response to or were intolerant to Remicade. The greatest proportion of patients had CD of the colon (82%) and ileum (77%).

7.4.2 Disposition:

The disposition is shown in the diagram below. Additional details can be found in the Clinical and Statistics Reviews.

[13] CDAI scores only for subjects ≥ 13 years old

Figure 7. Disposition (Study M06-806)



The diagram above is modified from: Hyams JS, Griffiths A, Markowitz J, et al., "Safety and Efficacy of Adalimumab for Moderate to Severe Crohn's Disease in Children", GASTROENTEROLOGY 2012;143:365–374.

Of the 192 patients total, 188 patients completed the 4 week induction period, 152 patients completed 26 weeks of treatment, and 124 patients completed 52 weeks of treatment. Fifty-one percent (51%) (48/95) of patients in the low maintenance dose group dose-escalated and 38% (35/93) of patients in the high maintenance dose group dose-escalated.

A higher number discontinued due to lack of efficacy in the low dose group (18) than the high dose group (11). Discontinuation due to AE's was similar in the low dose group (10) vs 12 (in the high dose group)

7.4.3 Efficacy Analyses:

All **"PCDAI remission"** rates presented below are "**un-adjusted PCDAI remission"** rates unless otherwise noted.

Primary Endpoint:

Low Dose vs. High Dose (Study M06-806): Although there was not a statistically significant difference between the two treatment doses (p = 0.075), a numerically greater proportion of subjects in the High-Dose treatment group achieved PCDAI clinical remission (defined as PCDAI ≤ 10) at Week 26 as compared with the Low-Dose treatment group (see table below). In addition, for the purpose of descriptive comparison to adult data using CDAI, the results of Study M02-404 are included.

Table 7. Primary Endpoint: Week 26 Clinical Remission (Study M06-806) (Study M02-404 Adult CD data included for descriptive comparison)

	Study M06-806				Study M02-404
	Low Dose* 20 or 10 mg eow N = 95 n/N (%)	High Dose# 40 or 20 mg eow N = 93 n/N (%)	Treatment Difference (95% CI)	p-value	40 mg eow N=260
Week 26					
Clinical Remission†	27/95 (**28.4%**)	36/93 (**38.7%**)	**10.3%** (-3.1%, 23.7%)	0.075	87/260 (**33.5%**)

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
†Clinical remission defined as PCDAI ≤ 10 (for Study M06-806 data); Clinical remission defined as CDAI ≤ 150 (for Study M02-404 data)
Study M06-806 results in table above are taken from the Clinical Review. Source: Sponsor's response to IR July 31, 2014. Study M02-404 results are taken from Page 236 of the M06-806 Clinical Study Report.

Descriptive Comparison to Study M02-404 CDAI Remission at Week 26: If one considers the PCDAI criteria for remission to be a 'higher bar' compared to the CDAI criteria for remission (see Section 7.3.6), then the results above suggest that the response rates for Humira in pediatric Crohn's disease are at least as high as the rates for Humira in adult Crohn's disease.

Applicant's Analysis using "Adjusted PCDAI Remission": The Applicant's analysis of the primary endpoint also included an external comparison (to Study M02-404). As the Applicant's analyses of the comparison using "adjusted PCDAI remission" data from this study to external data (from Study M02-404) (using CDAI) (for this endpoint) is considered exploratory only (see Sections 2.4.2 and 7.3.6), the results are not included here, but are included for completeness in Appendix 6.

First Three Ranked Secondary Endpoints:

Low Dose vs. High Dose: Comparison between treatment groups (Low- Dose vs High-Dose) of the proportion of subjects in PCDAI clinical remission at Week 52 , the proportion of subjects in PCDAI clinical response at Week 26 and the proportion of subjects in PCDAI clinical response at Week 52 did not show a statistically significant difference. However, there was a numerically higher proportion of subjects meeting each of these endpoints in the High-Dose treatment group (see the table below).

Table 8. First Three Ranked Secondary Endpoints (Study M06-806)

	Study M06-806			
	Low Dose* (20 or 10 mg eow) N = 95 n/N (%)	High Dose# (40 or 20 mg eow) N = 93 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Response§	46/95 (**48.4%**)	55/93 (**59.1%**)	**10.7%** (-3.4%, 24.9%)	0.073
Week 52				
Clinical Remission‡	22/95 (**23.2%**)	31/93 (**33.3%**)	**10.2%** (-2.6%, 23.0%)	0.100
Clinical Response§	27/95 (**28.4%**)	39/93 (**41.9%**)	**13.5%** (-0.01%, 27.0%)	0.038

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
‡ Clinical remission defined as PCDAI ≤ 10
§ Clinical response defined as reduction in PCDAI of at least 15 points from baseline
Table above is modified from the Clinical Review. Source: Sponsor's response to IR July 31, 2014

External Comparisons to Study M04-404: The Applicant did not propose or conduct analyses based on external comparisons to Study M04-404.

Fourth Ranked Secondary Endpoint:

Low Dose vs. High Dose: Although the proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders was numerically greater in the High-Dose as compared to the Low-Dose group, this difference was not statistically significant. See Table 13 below.

Table 9: Fourth-Ranked Secondary Endpoint: Clinical Remission at Week 26 (inWeek 4 Clinical Responders) (Study M06-806) (Study M02-404 Adult CD data included for descriptive comparison)

	Study M06-806				Study M02-404
	Low Dose* 20 or 10 mg eow N = 80 n/N (%)	High Dose# 40 or 20 mg eow N = 75 n/N (%)	Treatment Difference (95% CI)	p-value	40 mg eow N=172
Week 26					
Clinical Remission† at Week 26 (in Week 4 Clinical Responders§)	25/80 (**31.3%**)	33/75 (**44.0%**)	**12.8%** (-2.4%, 27.9%)	0.101	68/172 (**39.5%**)

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
†Clinical remission defined as PCDAI ≤ 10 (for Study M06-806 data); Clinical remission defined as CDAI ≤ 150 (for Study M02-404 data)
§Clinical response defined as reduction in PCDAI of at least 15 points from baseline (for Study M06-806 data); Clinical response defined as CDAI decrease of ≥70 (for Study M02-404 data)
Study M06-806 results in table above are taken from the Clinical Review. Source: Sponsor's response to IR July 31, 2014.
Study M02-404 results are taken from Page 236 of the M06-806 Clinical Study Report.

Descriptive Comparison to Study M02-404 CDAI Remission at Week 26 (in Week 4 Clinical Responders): If one considers the PCDAI criteria for remission to be a 'higher bar' compared to the CDAI criteria for remission (see Section 7.3.6), then the results above suggest that the

response rates for Humira in pediatric Crohn's disease are at least as high as the rates for Humira in adult Crohn's disease.

Applicant's Analysis using "Adjusted PCDAI Remission": The Applicant's analysis of this endpoint also included an external comparison (to Study M02-404). As the Applicant's analyses of the comparison using "adjusted PCDAI remission" data from this study to external data (from Study M02-404) (using CDAI) (for this endpoint) are considered exploratory only (see Sections 2.4.2 and 7.3.6), the results are not included here, but are included for completeness in Appendix 6.

Fifth Ranked Secondary Endpoint:

Only a descriptive comparison between Study M06-806 Week 4 PCDAI Remission and Study M02-404 CDAI remission is shown here.

Table 10: Fifth Ranked Secondary Endpoint: Clinical Remission at Week 4) (Study M06-806) (Study M02-404 Adult CD data included for descriptive comparison)

	Study M06-806* N=188	Study M02-404# N=854
Week 4		
Clinical Remission† at Week 4	52/188 (**27.7%**)	216/854 (**25.3%**)

*160 mg at Week 0 and 80 mg at Week 2 (for patients weighing ≥ 40 kg); and 80 mg at Week 0 and 40 mg at Week 2 (for patients weighing < 40 kg).
#80 mg at Week 0 and 40 mg at Week 2
†Clinical remission defined as PCDAI ≤ 10 (for Study M06-806 data); Clinical remission defined as CDAI ≤ 150 (for Study M02-404 data)
Study M06-806 results in table above are taken from the Clinical Review. Source: Sponsor's response to IR July 31, 2014.
Study M02-404 results are taken from Page 236 of the M06-806 Clinical Study Report.

Descriptive Comparison to Study M02-404 CDAI Remission at Week 4: If one considers the PCDAI criteria for remission to be a 'higher bar' compared to the CDAI criteria for remission (see Section 7.3.6), then the results above suggest that the response rates for Humira in pediatric Crohn's disease are at least as high as the rates for Humira in adult Crohn's disease.

Applicant's Analysis using "Adjusted PCDAI Remission": The Applicant's analysis of this endpoint was an external comparison (to Study M02-404). As the Applicant's analyses of the comparison using "adjusted PCDAI remission" data from this study to external data (from Study M02-404) (using CDAI) (for this endpoint) is considered exploratory only (see Sections 2.4.2 and 7.3.6), the results are not included here, but are included for completeness in Appendix 6.

7.4.4 Subgroup Analyses:

Prior Remicade Use:

When the results for the primary endpoint and the first five ranked secondary endpoints were subgrouped by prior Remicade use, the proportions of patients who met the respective endpoints were numerically higher in the subjects who were naïve to Remicade. It also appeared that the treatment differences were numerically higher in subjects who were naïve

to Remicade for each of the Week 26 and Week 52 endpoints below except for Week 26 Clinical Response (see the tables below).

Table 11: Primary Endpoint and First, Second, Third, and Fifth-Ranked Secondary Endpoints by Prior Remicade Use

	Induction Dose at Weeks 0 and 2[a] N = 188 n/N (%)			
Week 4				
Clinical Remission[d]			--	--
Prior Remicade use	18/83 (**21.7**)			
No prior Remicade use	34/105 (**32.4**)			
	Low Dose[c] (20 or 10 mg eow) N = 95 n/N (%)	High Dose[b] (40 or 20 mg eow) N = 93 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Remission[d]				
Prior Remicade use	8/41 (**19.5**)	7/42 (**16.7**)	**–2.85** (–19.40, 13.71)	0.736
No prior Remicade use	19/54 (**35.2**)	29/51 (**56.9**)	**21.68** (3.05, 40.31)	0.026
Clinical Response[e]				
Prior Remicade use	12/41 (**29.3**)	20/42 (**47.6**)	**18.35** (–2.19, 38.90)	0.086
No prior Remicade use	34/54 (**63.0**)	35/51 (**68.6**)	**5.66** (–12.45, 23.78)	0.541
Week 52				
Clinical Remission[d]				
Prior Remicade use	7/41 (**17.1**)	8/42 (**19.0**)	**1.97** (–14.57, 18.52)	0.815
No prior Remicade use	15/54 (**27.8**)	23/51 (**45.1**)	**17.32** (–0.82, 35.46)	0.065
Clinical Response[e]				
Prior Remicade use	9/41 (**22.0**)	11/42 (**26.2**)	**4.24** (–14.13, 22.61)	0.652
No prior Remicade use	18/54 (**33.3**)	28/51 (**54.9**)	**21.57** (3.01, 40.13)	0.026

a. For subjects ≥ 40 kg, induction dose was 160 mg (at Week 0) and 80 mg (at Week 2). For subjects weighing < 40 kg, the induction dose was 80 mg (at Week 0) and 40 mg (at Week 2).
b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
d. Clinical remission defined as PCDAI ≤ 10.
e. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.
Table above is modified from the Clinical Review. Source: Sponsor's response to IR July 31, 2014.

Table 12. Fourth-Ranked Secondary Endpoint by Prior Remicade Use (Study M06-806)

	Low Dose* 20 or 10 mg eow N = 80 n/N (%)	High Dose# 40 or 20 mg eow N = 75 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Remission† at Week 26 (in Week 4 Clinical Responders§)				
Prior Remicade use	7/32 (**21.9**)	6/32 (**18.8**)	**-3.13** (-22.82, 16.57)	0.756
No prior Remicade use	18/48 (**37.5**)	27/43 (**62.8**)	**25.29** (5.38, 45.20)	0.016

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
†Clinical remission defined as PCDAI ≤ 10
§Clinical response defined as reduction in PCDAI of at least 15 points from baseline
Table above is taken from the Response to IR from the Sponsor dated July 31, 2014

Body Weight Category:

When the results for the primary endpoint and the first five ranked secondary endpoints were subgrouped by Body Weight Category (< 40 kg or ≥ 40 kg), a similar proportion of patients in each of the Body Weight Category subgroups met the respective endpoints (see the tables below). The treatment differences were similar between the two Body Weight categories except for Clinical Response at Week 26 (higher treatment difference in the high Body Weight category) and Clinical Remission at Week 52 (higher treatment difference in the low Body Weight category) (see the tables below).

Table 13: Summary of Subjects in Clinical Remission or Clinical Response at Weeks 4, 26, and 52 by Treatment Group and Body Weight Category

	Induction Dose at Weeks 0 and 2[a] N = 188			
Week 4				
Clinical Remission[d]			--	--
< 40 kg at baseline	16/67 (**23.9**)			
≥ 40 kg at baseline	36/121 (**29.8**)			
	Low Maintenance Dose[c] (20 or 10 mg eow) N = 95 n/N (%)	High Maintenance Dose[b] (40 or 20 mg eow) N = 93 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Remission[d]				
< 40 kg at baseline	9/35 (**25.7**)	11/32 (**34.4**)	**8.66** (–13.26, 30.58)	0.206
≥ 40 kg at baseline	18/60 (**30.0**)	25/61 (**41.0**)	**10.98** (–5.95, 27.92)	0.202
Clinical Response[e]				
< 40 kg at baseline	16/35 (**45.7**)	16/32 (**50.0**)	**4.29** (–19.64, 28.21)	0.394
≥ 40 kg at baseline	30/60 (**50.0**)	39/61 (**63.9**)	**13.93** (–3.54, 31.41)	0.115
Week 52				
Clinical Remission[d]				
< 40 kg at baseline	6/35 (**17.1**)	10/32 (**31.3**)	**14.11** (–6.24, 34.45)	0.066
≥ 40 kg at baseline	16/60 (**26.7**)	21/61 (**34.4**)	**7.76** (–8.59, 24.11)	0.421
Clinical Response[e]				
< 40 kg at baseline	10/35 (**28.6**)	13/32 (**40.6**)	**12.05** (–10.61, 34.72)	0.113
≥ 40 kg at baseline	17/60 (**28.3**)	26/61 (**42.6**)	**14.29** (–2.56, 31.14)	0.123

a. For subjects weighing ≥ 40 kg, induction dose was 160 mg (at Week 0) and 80 mg (at Week 2). For subjects weighing < 40 kg, the induction dose was 80 mg (at Week 0) and 40 mg (at Week 2).
b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
d. Clinical remission defined as PCDAI ≤ 10.
e. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.
Table above is modified from the Clinical Review. Source: Sponsor's response to IR on 31 July 2014

Table 14: Fourth-Ranked Secondary Endpoint by Baseline Weight Category (Study M06-806)

	Low Dose* 20 or 10 mg eow N = 80 n/N (%)	High Dose# 40 or 20 mg eow N = 75 n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Remission† at Week 26 (in Week 4 Clinical Responders§)				
< 40 kg at baseline	9/31 (**29.0**)	11/27 (**40.7**)	**11.71** (-12.76, 36.18)	0.349
≥ 40 kg at baseline	16/49 (**37.5**)	22/48 (**45.8**)	**13.18** (-6.08, 32.44)	0.184

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
†Clinical remission defined as PCDAI ≤ 10
§Clinical response defined as reduction in PCDAI of at least 15 points from baseline
Table above is taken from the Response to IR from the Sponsor dated July 31, 2014

7.4.5 Discussion

The main review issues regarding the evaluation of efficacy were whether pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults; and what the appropriate dose should be for the pediatric indication.

Using the partial extrapolation approach (as described above in Section 7.1), a combination of clinical response data (using clinical remission rates) and PK data were the basis for extrapolation to support efficacy in pediatric patients. The Clinical Pharmacology Reviewers' conclusions are integrated into the discussion of efficacy data and dose selection below.

Comparison of Pediatric to Adult Data: Although the pediatric data is based on the PCDAI and the adult data is based on the CDAI, PCDAI remission has been considered to be a "higher bar" than CDAI remission (see Section 7.3.6).[14] Thus, it seems reasonable to interpret similar rates of remission in the adult study and pediatric study using the respective instruments as demonstration that the remission rates for Humira in pediatric Crohn's disease are at least as high as the remission rates for Humira in adult Crohn's disease.

Induction: There was an exposure-response relationship (for clinical remission) in the adult CD studies for induction. However, an exposure-response relationship (for clinical remission) could not be established in the pediatric CD study for induction. The Week 4 remission rate in the pediatric trial appeared to be similar to the corresponding rate in the adult CD trial (see Section 7.4.3). The Clinical Pharmacology Reviewers pointed to this similarity as well as the similarity in the trough concentrations between the pediatric and adult trials as evidence supporting the appropriateness of the proposed pediatric CD induction dose.

[14] Clinical Team Leader Memo by John Hyde (Humira for Adult CD) dated February 27, 2007.

Maintenance: An exposure-response relationship (for clinical remission) could not be established in the adult CD study for maintenance. However, there was an exposure-response relationship (for clinical remission) in the pediatric CD study for maintenance. In addition, there appeared to be a dose-response relationship for the primary endpoint and the first four secondary endpoints; both the Clinical Reviewer and the Statistics Reviewer commented that although there was no statistically significant difference between the two groups, there was a trend in favor of the high dose for each of these endpoints. The Clinical Pharmacology Reviewers commented that pediatric subjects receiving the Low Dose had generally lower steady state exposure than that observed in adult subjects receiving the approved dose. The Clinical Pharmacology Reviewers pointed to all of these data as evidence supporting the appropriateness of the High Dose for maintenance. At the High Dose in the pediatric trial, remission rates at Week 26 overall and in the subgroup of Week 4 responders appeared to be similar to the corresponding rates in the adult CD trial (see Section 7.4.3). Taken together, these data provide supportive evidence of the effectiveness of the Humira High Dose for maintenance of remission in pediatric CD.

7.5 Final Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical Efficacy standpoint.

The proposed induction dosing regimen is acceptable. The High Dose maintenance regimen should be the recommended maintenance dosing regimen.

See also Section 5.8 (Final Recommendation in the Clinical Pharmacology section).

8. Safety

The reader is referred to the Clinical Review by Marjorie Dannis, for complete information.

8.1 Overview of Data Evaluated for Safety

8.1.1 Analysis Populations

The analysis populations below include data from Study M06-807 (an extension study that enrolled patients completed Study M06-806).

Four analysis sets were used for the review of safety:
(1) Any Adalimumab Set (N=192): All subjects who received at least one dose in Studies M06-806 and M06-807.
(2) M06-806 Safety Analysis Set (N=188): All randomized subjects who received at least one dose of DB adalimumab
(3) Dose Escalation Set (N = 118): All subjects who dose-escalated from eow to ew dosing in Study M06-806 or Study M06-807 or subjects who were in the Low Dose group at Week 52 in Study M06-806 and rolled over to the high OL eow dose in Study M06-807

(4) No Dose Escalation Set (N = 74): All subjects who did not have dose-escalation in Study M06-806 or Study M06-807.

8.1.2 Exposure

Across both studies, a total of 192 pediatric subjects with CD have been exposed to at least 1 dose of adalimumab as of 31 January 2013, for a cumulative exposure of 404 patient years (PYs). Of these subjects, 115 had at least 12 months of adalimumab exposure, 82 had at least 24 months of exposure, 75 had at least 36 months of exposure, and 40 had at least 48 months of exposure. The median exposure was 434 days (range of 14 to 1,977 days).

8.2 Safety Findings

8.2.1 Deaths

No deaths were reported in Study M06-806 or Study M06-807.

8.2.2. Serious Adverse Events

Any Adalimumab Set:

Of the 192 patients that received Humira, 86 (45%) had at least one SAE. The large majority of these were CD flare or other events referable to the GI system or underlying disease.

CD flare was reported as an SAE in 57 patients (30%), anemia in 4 (2%), abdominal abscess in 3 (2%), anal abscess in 3 (2%), abdominal pain in 2 (1%), tachycardia in 2 (1%), gastritis in 2 (1%), pneumonia in 2 (1%), and small intestinal obstruction in 2 (1%)(see the table below). All other SAEs were reported in only 1 patient each (see the Clinical Review for listing of other SAE's).

Table 15. SAE's Reported in ≥ 1% of Patients (Any Adalimumab Set)

System Organ Class Preferred Term	Any Adalimumab Set N=192 n (%)
Blood and Lymphatic System Disorders	
Anemia	4 (2%)
Cardiac Disorders	
Tachycardia	2 (1%)
Gastrointestinal Disorders	
Crohn's disease	57 (30%)
Abdominal pain	2 (1%)
Gastritis	2 (1%)
Small intestinal obstruction	2 (1%)
Infections and Infestations	
Abdominal abscess	3 (2%)
Anal abscess	3 (2%)
Pneumonia	2 (1%)

The table above is modified from the Clinical Review. Source: Summary of Clinical Safety Pages 89-91.

The Clinical Reviewer commented that whether anemia, abdominal abscess, anal abscess, abdominal pain, gastritis, and small intestinal obstruction were actually treatment related is difficult to discern because the events could have been secondary to the subject's underlying disease process.

See Section 8.2.4 below for discussion of AE's of special interest.

Safety Analysis Set (DB Period of Study M06-806):

In the Safety Analysis Set (DB Period of Study M06-806), 19 (20%) had at least one SAE in the Low Dose group and 22 (24%) had at least one SAE in the High Dose group. The large majority of these were CD flares in each of the arms; there was a slightly higher proportion in the Low Dose arm. Although there were four cases of anemia reported in the High Dose arm and zero in the Low Dose arm, the Clinical Reviewer noted that these four patients had a history of anemia and the events resolved within a few days. See the table below showing SAE's reported in > 1 patient in either dose arm; see Appendix 7 of this CDTL Review for the table showing all SAE's reported.

Table 16. SAE's Reported in > 1 Patient in Either Dose Arm (DB Period of Study M06-806)

System Organ Class Preferred Term	Low Dose* 20 or 10 mg eow N = 95 n (%)	High Dose# 40 or 20 mg eow N = 93 n (%)
Blood and Lymphatic System Disorders		
Anemia	0	4 (4%)
Gastrointestinal Disorders		
Crohn's disease	15 (16%)	12 (13%)

*Low Maintenance Dose: 10 mg eow (for patients weighing < 40 kg) and 20 mg eow (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg eow (for patients weighing < 40 kg) and 40 mg eow (for patients weighing ≥ 40 kg).
Table above is modified from a tables found on Page 366 and Pages 1467-1468 of the M06-806 Study Report.

See Section 8.2.5 below for discussion of AE's subgrouped by body weight category.

8.2.3 Dropouts and/or Discontinuations

Any Adalimumab Set:

Of the 192 patients that received Humira, 55 (29%) had AEs leading to discontinuation. The large majority of these were CD flare or other events referable to the GI system or underlying disease.

CD flare led to the discontinuation of 38 patients (20%), abdominal pain, diarrhea, and abdominal abscess each led to the discontinuation of 2 patients (1%). See the table below.

Table 17. AE's Leading to Discontinuation in ≥ 1% of Patients (Any Adalimumab Set)

System Organ Class Preferred Term	Any Adalimumab Set N=192 n (%)
Gastrointestinal Disorders	
Crohn's disease	38 (20%)
Abdominal pain	2 (1%)
Diarrhea	2 (1%)
Infections and Infestations	
Abdominal abscess	2 (1%)

The table above is modified from a table in the Summary of Clinical Safety Pages 97-98.

See Section 8.2.4 below for discussion of AE's of special interest.

Safety Analysis Set (DB Period of Study M06-806):

In the Safety Analysis Set (DB Period of Study M06-806), 12 (13%) discontinued due to an AE in the Low Dose group and 15 (16%) discontinued due to an AE in the High Dose group. The large majority of these were CD flares in each of the arms, 10 (10.5%) in Low Dose group and 11 (12%) in the High Dose group. All other AE's leading to discontinuation were in one patient each; see Appendix 8 of this CDTL Review.

See Section 8.2.5 below for discussion of AE's subgrouped by body weight category.

8.2.4 Adverse Events of Special Interest

No malignancies, hepatosplenic T-cell lymphoma (HSTCL), leukemia, melanoma, cutaneous vasculitis, diverticulitis, intestinal perforation, MI, CVA, pulmonary embolism, demyelinating disease, Stevens-Johnson syndrome, erythema multiforme, CHF, or interstitial lung disease AEs were reported.

Serious Infections: Of the 192 patients that received Humira, 21 (11%) had at least one serious infection. Abdominal abscess and anal abscess were each reported as serious infections in 3 subjects (2%), and pneumonia was reported as a serious infection in 2 subjects (1%); all other serious infections were reported in only 1 patient each (including viral infection, device-related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis) (see the Clinical Review for full listing of other serious infections). The

Clinical Reviewer commented that whether abdominal abscess and anal abscess were actually treatment related is difficult to discern because the events could have been secondary to the subject's underlying disease process. See Section 12 of this CDTL Review for labeling recommendations.

Opportunistic Infections: Of the 192 patients that received Humira, 8 (4%) reported opportunistic infection related AEs. These included disseminated histoplasmosis, Aeromona infection, oral candidiasis (four patients including one patient with multiple episodes), esophageal candidiasis, and fungal esophagitis. It should be noted that opportunistic infections are currently represented in the labeling.

Injection Site Reaction-Related AE's: Of the 192 patients that received Humira, 42 (22%) reported injection site reaction-related AE's; the most frequently reported of these were injection site reaction (22 patients; 12%), and injection site pain (15 patients; 8%). During the induction phase, 22 (11.5%) reported injection site reaction-related AE's; the most frequently reported of these were injection site pain (12 patients; 6%), and injection site reaction (10 patients; 5%).[15] See Section 12 of this CDTL Review for labeling recommendations.

Lupus-Like Syndrome: One patient, a 14-year-old white female, experienced a serious TEAE of systemic lupus erythematosus during Study M06-807 (Day 534 of adalimumab treatment) The subject experienced worsening of pre-existing arthritis on Day 522 and increased CRP on Day 534. The subject's ANA titer was negative (< 1:40) on Day 1 and was > 1:2560 on Day 534.The last dose of study drug was administered on Day 534. The subject discontinued study drug due to the event. The event was ongoing as of Day 667. It should be noted that lupus-like syndrome is currently represented in the labeling.

Allergic Reaction Related: Of the 192 patients that received Humira, 40 (21%) experienced allergic reaction related AE's; rash, hypersensitivity, urticaria, and erythema were the most frequently reported allergic reaction related AEs, occurring in 7%, 4%, 4%, and 3% of patients, respectively. It should be noted that allergic reactions are currently represented in the labeling.

Hematologic-Related Events: Of the 192 patients that received Humira, 30 (16%) experienced a hematologic related AE. Seventeen subjects (9%) had anemia, and nine subjects (5%) had leukopenia. Four subjects who all had a history of anemia experienced SAEs of anemia, which resolved within a few days. It should be noted that leukopenia is currently represented in the labeling.

Additional AE's of special interest are described in the Clinical Review.

See Section 8.2.5 below for discussion of AE's subgrouped by body weight category.

[15]Source: Page 1572 of the M06-806 Study Report

8.2.5 AE's Subgrouped by Body Weight Category

Based on comparison of rates of overall AEs (in the M06-806 DB Period; Safety Analysis Set) within each of the Body Weight Categories, it initially appeared that there were higher proportions of SAEs, Severe AEs, AEs leading to discontinuation, and Infectious AEs with the High Dose than the Low Dose in the Body Weight < 40kg category (see the table below). Such a trend was not observed in the Body Weight ≥ 40kg category (see the table below).

Table 18. AE's by Body Weight Category (Safety Analysis Set; DB Period of Study M06-806)

	Weight < 40 kg		Weight ≥ 40 kg	
	10 mg dose N = 31	20 mg dose N = 29	20 mg dose N = 64	40 mg dose N = 64
Any adverse event	24 (77.4)	26 (89.7)	57 (89.1)	60 (93.8)
At least possibly drug-related[a]	11 (35.5)	9 (31.0)	26 (40.6)	30 (46.9)
Severe adverse event	4 (12.9)	9 (31.0)	7 (10.9)	10 (15.6)
Serious adverse event	4 (12.9)	10 (34.5)	15 (23.4)	12 (18.8)
Leading to discontinuation of study drug	3 (9.7)	8 (27.6)	9 (14.1)	7 (10.9)
At least possibly drug-related SAE[a]	0	0	2 (3.1)	1 (1.6)
Infectious adverse event	14 (45.2)	19 (65.5)	33 (51.6)	37 (57.8)
Serious infections	1 (3.2)	2 (6.9)	2 (3.1)	3 (4.7)

The table above is modified from a table found on Page 353 of the M06-806 Study Report.

In order to exclude the possibility that the apparent difference in AE rates was due to dose-escalation, an additional table was generated excluding patients who dose-escalated (see table below). Based on comparison of rates of overall AEs in the Body Weight < 40 kg group (in the M06-806 DB Period; Safety Analysis Set) excluding subjects who dose-escalated, it also initially appeared that there were higher proportions of SAEs, Severe AEs, AEs leading to discontinuation, and Infectious AEs with the High Dose than the Low Dose in the Body Weight < 40kg category (see the table below).

Table 19. AE's in Subjects who did not Dose Escalate with Body Weight < 40 kg (DB Period of Study M06-806)

AE Category	ADA Low 10 mg N = 12	ADA High 20 mg N = 19
Any adverse event	10 (83.3)	17 (89.5)
At least possibly drug-related[b]	5 (41.7)	6 (31.6)
Severe adverse event	3 (25.0)	8 (42.1)
Serious adverse event	2 (16.7)	7 (36.8)
Leading to discontinuation of study drug	2 (16.7)	7 (36.8)
At least possibly drug-related SAE[b]	0	0
Infectious adverse event	6 (50.0)	13 (68.4)
Serious infections	0	2 (10.5)

The table above is modified from the Clinical Review. Source: Page 54 of the Response to Feb 21, 2014 IR.

The Clinical Reviewer reviewed each of the cases, and concluded that the apparent differences in AEs rates (in the table above) may not be significant because many of the AEs

in the High Dose group were secondary to worsening of CD or upper respiratory tract infection (URI) / nasopharyngitis. The CD cases may represent underlying disease; URI/nasopharyngitis events are common in the population studied and may not be due to the study drug. The Clinical Reviewer also commented that the number of subjects in each treatment group was small (N=12; N=19) and the numbers were not balanced, so that it would be difficult to draw accurate conclusions from this data. See the Clinical Review for details of the individual cases.

8.2.6. Common Adverse Events

Any Adalimumab Set:

Of the 192 patients that received Humira, 189 (98%) had at least one AE. The majority of these were CD flare or other events referable to the GI system or underlying disease. The next largest group of events were upper respiratory tract infection / nasopharyngitis. See the table below.

Table 20. AE's Reported by ≥ 10% of Subjects by Descending Order of Frequency (Any Adalimumab Set)

MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Crohn's disease	100 (52.1)
Headache	51 (26.6)
Upper respiratory tract infection	41 (21.4)
Nasopharyngitis	39 (20.3)
Diarrhoea	33 (17.2)
Nausea	32 (16.7)
Oropharyngeal pain	32 (16.7)
Pyrexia	32 (16.7)
Abdominal pain	29 (15.1)
Vomiting	29 (15.1)
Cough	28 (14.6)
Arthralgia	25 (13.0)
Fatigue	22 (11.5)
Injection site reaction	22 (11.5)
Abdominal pain upper	21 (10.9)
Constipation	21 (10.9)
Viral infection	21 (10.9)

Table above is modified from the Clinical Review. Source: Pages 80-81 of the Summary of Clinical Safety.

Safety Analysis Set (DB Period of Study M06-806):

In the Safety Analysis Set (DB Period of Study M06-806), 81 (85%) had at least one AE in the Low Dose group and 86 (92.5%) had at least one AE in the High Dose group. The plurality of these in each of the arms were CD flares or other events referable to the GI

system or underlying disease. The next largest group of events were upper respiratory tract infection / nasopharyngitis in each of the arms. No clear trends in incidence of specific AE's were appreciated between the High Dose and Low Dose groups. See the table below.

Table 21. AE's Reported in ≥5% of Patients in the Total Group by Descending Frequency of Total Adalimumab (DB Period of Study M06-806)

	Adalimumab, n (%)		
	Low-Dose 20 mg or 10 mg Eow N = 95	High-Dose 40 mg or 20 mg Eow N = 93	Total N = 188
Preferred Term	n (%)	n (%)	n (%)
Crohn's disease	30 (31.6)	23 (24.7)	53 (28.2)
Headache	20 (21.1)	16 (17.2)	36 (19.1)
Nasopharyngitis	11 (11.6)	9 (9.7)	20 (10.6)
Upper respiratory tract infection	10 (10.5)	10 (10.8)	20 (10.6)
Pyrexia	8 (8.4)	10 (10.8)	18 (9.6)
Oropharyngeal pain	8 (8.4)	9 (9.7)	17 (9.0)
Diarrhea	9 (9.5)	8 (8.6)	17 (9.0)
Nausea	6 (6.3)	10 (10.8)	16 (8.5)
Cough	7 (7.4)	9 (9.7)	16 (8.5)
Vomiting	10 (10.5)	6 (6.5)	16 (8.5)
Abdominal pain	6 (6.3)	9 (9.7)	15 (8.0)
Arthralgia	4 (4.2)	8 (8.6)	12 (6.4)
Rhinorrhea	8 (8.4)	3 (3.2)	11 (5.9)
Abdominal pain upper	3 (3.2)	7 (7.5)	10 (5.3)
Rash	5 (5.3)	5 (5.4)	10 (5.3)
Viral infection	6 (6.3)	4 (4.3)	10 (5.3)

The table above is taken from Page 306 of the M06-806 Study Report.

8.2.7. Summary

There was no clear trend of higher incidence of AEs with increasing Humira dose or with Body Weight category seen in the pediatric CD studies.

No new safety signals were identified in review of the sBLA. Known events associated with the use of Humira appear to be adequately represented in current labeling.

See labeling recommendations in Section 12 of this CDTL Review.

8.3 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Orphan Status and PREA Applicability: Orphan status for pediatric CD was granted October 19, 2006.[16] This was before the PREA PMC was issued (February 27, 2007) in the approval letter for the adult CD indication.[17] Section 50513(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 35513(k)) states that: "[u]nless the Secretary requires otherwise by regulation, this section [PREA] does not apply to any drug for an indication for which orphan designation has been granted under section 526 [of the Act]." Thus, a PREA PMC should not have been issued at the time of the approval for adult CD. A letter was sent to the applicant on February 11, 2014 indicating that PREA did not apply to this application. Also, for this reason, the current sBLA was not presented to the Pediatric Research Committee (PeRC).

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 Susan Leibenhaut, dated May 12, 2014 for complete information.

Sites 37027, 34218 , and 8916 were selected because each had a high percentage of the subjects in Study M06-806 relative to other sites. Another reason for selecting Site 37027 was that it had a low proportion of patients meeting the primary endpoint in the high dose

[16] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=230306 (accessed August 31, 2014)
[17] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2007/125057s089Ltr.pdf (accessed August 31, 2014)

group (0/8) compared to the low dose group (2/5). Another reason for selecting Sites 34218 and 8916 was that each of these sites has never been inspected according to OSI.

Overview of Inspections and Final Classifications:

An overview of the three sites inspected and final classifications are presented in the table below.

Table 22. Overview of Sites Inspected and Final Classifications

Investigator / Location / Site No.	Study	No. Pts*	Final Classification
Joshua D. Noe / Milwaukee, WI / 37027	M06-806	10	NAI
William Faubion / Rochester, MN / 34218	M06-806	13	NAI
John M. Howard / London, Ontario Canada / 8916	M06-806	10	NAI

*Number of subjects enrolled.

Inspector's Key Findings:

The Inspector's key findings are summarized below for each of the three site inspections (by Clinical Investigator (CI).

Joshua D. Noe, M.D.: There was evidence of under-reporting of two AEs (upper respiratory infection and gastroenteritis) (considered mild in severity and probably not related to study drug) for one subject in the low dose group. The OSI Reviewer concluded that the unreported adverse events appear to be an isolated instance; and that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

William Faubion, Jr. M.D.: No significant regulatory violations were noted and no Form FDA 483 was issued. There was no evidence of underreporting of AE's, and the source data for the primary efficacy data were able to be verified at the site. The OSI Reviewer concluded that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

John M. Howard, M.D.: No significant regulatory violations were noted and no Form FDA 483 was issued. There was no evidence of underreporting of AE's, and the source data for the primary efficacy data were able to be verified at the site. The OSI Reviewer concluded that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

Final Conclusion:

OSI concluded that the data generated by these sites are considered reliable in support of the application.

11.3 Human Factors Studies Reviewed by CDRH

See the CDRH Human Factors Premarket Evaluation Team (HFPMET) Review by Quynh Nguyen for full information.

The CDRH HFPMET Reviewer noted that two study reports were included in this supplement of the BLA: (1) Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report; and (2) Dosing Comprehension for Humira for Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report.

The CDRH HFPMET Review noted the following results of these studies:

> "The Pharmacist and Pharmacy Technician Human Factors Validation Study Report: showed errors and close calls where the pharmacy technician cohort dispensed incorrect medication or would have dispensed incorrect medication if the pharmacists did not correct the errors respectively. For those errors that were not corrected by the pharmacists, we are most concerned with errors where the technicians dispensed Humira pens instead of Crohn's disease starter package, adult starter package instead of pediatric package, and small pediatric starter package instead of large pediatric starter package. The HFMPET Reviewer believes that if these errors were to occur in actual use, they could lead to delay of therapy or sub-optimal treatment. "
>
> "The Patients and Caregivers Validation Study Report showed 1 participant failed to complete all three tasks (initial dose, second dose, and maintenance dose), 2 participants failed to complete task 2, and 1 participant failed to complete task 3. We are concerned that these errors can result in sub-optimal treatment (i.e., underdose and overdose)."

The CDRH HFPMET Review noted that the issues above were resolved as follows:

> "For the Pharmacist and Pharmacy Technician Human Factors Validation Study, Abbvie (1) provided copies of all prescriptions that were used in the study, (2) clarified the differences between the packaging of the commercially available Humira products and the packaging of the proposed product, (3) discussed the clinical impact on user making packaging selection errors, (4) supplied additional subjective data which revealed that the errors and close calls observed were not found to be directly related to the product packages or package designs, (5) provided a discussion on how the product labeling has been optimized to ensure safe and effective use."
>
> "For the Patients and Caregivers Validation Study, Abbvie provided updated product labeling including Instructions for Use for patients to address the concern that participants did not review the Starter Package Information and Calendar. In addition, Abbvie supplied additional subjective data which indicated that the errors observed were not found to be directly related to the Starter Package labeling. Abbvie believes that the dosing instructions for the PCD Starter Packages have been optimized in particular; the Starter Package contains an example calendar, which was tested during

the human factors validation study and contains dosing instructions to assist the patient with induction dosing."

See Section 12 of this CDTL Review for the labeling revisions to the Instructions for Use described above.

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):
  - The Applicant's proposed wording (b) (4) was replaced with "inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate" to describe the population that was studied.

- Dosage and Administration (Section 2.4 of Label):
  - The Applicant's proposal for a weight-tiered induction and maintenance dose (lower dose for patients < 40 kg; higher dose for patients ≥ 40 kg) was accepted.
  - The Applicant's proposal to recommend the high maintenance dose[18] studied in the clinical trial (rather than the low maintenance dose[19] studied in the clinical trial) was accepted.
  - (b) (4)
  -

- Adverse Reactions (Section 6.1 of Label):
  - The Applicant's proposal to include the most common adverse reactions in the induction phase (injection site pain and injection site reaction) and the proportions of patients experiencing those adverse reactions was accepted.
  - The Applicant's proposal to include the proportion of patients experiencing an infection, and to include specific infections (upper respiratory tract infection and nasopharyngitis) was accepted.

(b) (4)

- The Applicant's proposal to include the proportion of patients experiencing a serious infection, and to include specific serious infections (viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis) was accepted.
- The Applicant's proposal to include the proportion of patients experiencing allergic reactions and to provide a general description of these reactions as non-serious and primarily localized reactions was accepted.

➢ Clinical Studies (Section 14.6 of Label):

- (b) (4)
- The proportions of patients receiving corticosteroids at baseline and receiving immunomodulators at baseline were included; also, the proportion of patients with loss of response or intolerance to a TNFα-antagonist was included.
- (b) (4)

Medication Guide:

➢ What is HUMIRA?: The wording below proposed by the Applicant was accepted as part of the bulleted list (of a number of Humira approved indicated populations) following "To reduce the signs and symptoms of:"

> "moderate to severe Crohn's disease (CD) in children 6 years and older when other treatments have not worked well enough."

It should be noted that this statement for pediatric CD parallels the previously existing wording here for adult CD ("moderate to severe Crohn's disease (CD) in adults when other treatments have not worked well enough.")

Instructions for Use:

In the first paragraph of each of the presentations of Humira (i.e., single-use pen, and single-use prefilled syringe), the following was added:

> "It is also important to talk to your doctor to be sure you understand your HUMIRA dosing instructions. To help you remember when to inject HUMIRA, you can mark your calendar ahead of time."

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 DMA Label and 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 an Approval action. This Reviewer concurs with the approval recommendation from each of the disciplines.

13.2 Risk Benefit Assessment

The benefit of Humira for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate has been established in the clinical trials. The safety profile was acceptable based on what was found in the clinical trials.

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.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

None of the primary review disciplines had recommendations for additional postmarketing requirements.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

None of the primary review disciplines had recommendations for postmarketing commitments.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: Pertinent Results from Humira for Adult CD Trials

The following is summarized from the Humira for Adult CD TL Memo by John Hyde, and the Humira for Adult CD Clinical Review by Li-ching Liang.

A. Phase 2/3 Induction Trial (Study M02-403)

Design Overview: Randomized, double-blind, placebo-controlled, dose-exploration induction study in 299 adult CD patients. The doses administered were 40 mg/20 mg (40 mg at Day 1 followed by 20 mg two weeks later), 80 mg/40 mg (80 mg at Day 1 followed by 40 mg two weeks later), and 160 mg/80 mg (160 mg at Day 1 followed by 80 mg two weeks later).

Overview of Results: Results of the trial are summarized in the table below.

Table 23. Pairwise Comparisons in Induction of Clinical Remission (Study M02-403)

Full Analysis Set (N=299)				
Adalimumab Dose/ Time Point in Study	Adalimumab n (%)	Placebo (N=74) n (%)	Difference[a] (95% CI)	Treatment Effect p-value
40 mg/20 mg (N=74)				
Week 1	12 (16)	5 (7)	9.5 (-0.7, 19.6)	0.071
Week 2	10 (14)	10 (14)	0.0 (-11.0, 11.0)	1.000
Week 4	13 (18)	9 (12)	5.4 (-6.0, 16.8)	0.355
Week 4 (LOCF)	13 (18)	9 (13)	5.3 (-6.3, 16.9)	0.373
80 mg/40 mg (N=75)				
Week 1	10 (13)	5 (7)	6.6 (-3.0, 16.2)	0.182
Week 2	15 (20)	10 (14)	6.5 (-5.5, 18.4)	0.289
Week 4	18 (24)	9 (12)	11.8 (-0.4, 24.0)	0.061
Week 4 (LOCF)	18 (25)	9 (13)	12.2 (-0.3, 24.7)	0.060
160 mg/80 mg (N=76)				
Week 1	12 (16)	5 (7)	9.0 (-1.0, 19.0)	0.081
Week 2	18 (24)	10 (14)	10.2 (-2.2, 22.5)	0.110
Week 4	27 (36)	9 (12)	23.4 (10.3, 36.4)	0.001
Week 4 (LOCF)	27 (36)	9 (13)	23.0 (9.8, 36.2)	0.001
All adalimumab (N=225)				
Week 1	34 (15)	5 (7)	8.4 (1.0, 15.7)	0.064
Week 2	43 (19)	10 (14)	5.6 (-3.7, 14.9)	0.274
Week 4	58 (26)	9 (12)	13.6 (4.2, 23.0)	0.015
Week 4 (LOCF)	58 (26)	9 (13)	13.6 (4.0, 23.2)	0.017

a. Difference refers to the difference between the proportion (%) of adalimumab-treated subjects achieving clinical remission compared with the placebo-treated subjects.

B. Phase 3 Induction Trial (Study M04-691)

Design Overview: This was a randomized, double-blind, placebo-controlled, induction study at 52 sites in 325 adult CD patients. Patients were required to have either initially responded to infliximab but lost response, or to be intolerant to infliximab, according to specific criteria described in the protocol. The dosing regimen was 160/80 mg (i.e., 160 mg on Day 1

followed by 80 mg two weeks later). The primary endpoint was clinical remission (CDAI < 150) at Week 4.

Overview of Results: Results of the trial are summarized in the table below.

Table 24. Clinical Remission at Week 4 (Study M04-691)

	Treatment Group n (%)			
	Placebo (N=166)	Adalimumab 160/80 mg (N=159)	Difference in Proportions (95% CI)	p-value
Week 4 Visit	12 (7)	34 (21)	14.2 (6.7, 21.6)	<0.001

C. Phase 3 Maintenance Trial (Study M02-404)

Design Overview: This was a randomized, double-blind, placebo-controlled induction and maintenance study of 854 adult CD patients for 56 weeks. Subjects were given open-label adalimumab 80 mg at Week 0 and 40 mg at Week 2. Patients who met criteria for response (CDAI decrease of ≥70) at Week 4 were randomized to maintenance treatment. At Week 4, subjects were stratified by responder status and previous anti-TNF use and then randomized 1:1:1 to adalimumab 40 mg ew, adalimumab 40 mg eow, or placebo. The primary endpoint was clinical remission (CDAI < 150) at Week 26.

Overview of Results: Results of the trial are summarized in the table below.

Table 25. Clinical Remission at Week 26 and Week 56 in Study M02-404 (mITT dataset)

		Placebo	Adalimumab eow	Adalimumab ew
		N=170	N=172	N=157
Visit			n (%)	
Week 26		29 (17.1)	68 (39.5)	73 (46.5)
Week 56		20 (11.8)	62 (36.0)	65 (41.4)
Visit	Treatment Comparison	Difference in Proportions	95% CI	p-value[a]
Week 26	Adalimumab 40 mg eow *vs.* placebo	22.5	(13.2, 31.7)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* placebo	29.4	(19.8, 39.1)	< 0.001
Week 26	Adalimumab 40 mg ew *vs.* adalimumab 40 mg eow	7.0	(-3.7, 17.7)	0.220
Week 56	Adalimumab 40 mg eow *vs.* placebo	24.3	(15.6, 32.9)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* placebo	29.6	(20.5, 38.7)	< 0.001
Week 56	Adalimumab 40 mg ew *vs.* adalimumab 40 mg eow	5.4	(-5.2, 15.9)	0.344

eow = every other week; ew = weekly; CI = confidence interval

a. The p-value is from CMH test stratified by previous anti-TNF use.

Note: Subjects without CDAI assessments at Weeks 26 or 56 were to be classified as remission "failures."

Cross Reference: Section 14, Table 14.2__1.1.2.

APPENDIX 2: Comparison of Assessments Included in CDAI and PCDAI Instruments

The table below summarizes the differences in the assessments included in the CDAI and PCDAI Instruments.

Table 26. Comparison of Assessments Included in the CDAI and PCDAI Instruments

Variable	CDAI	PCDAI
Abdominal Pain	√	√
Stool Characteristics	√	√
General Well-being	√	√
Extraintestinal Manifestations	√	√
Abdominal Exam	√	√
Body Weight	√	Assessed as growth
Height/ Growth	Not included	√
Hematocrit	√	√
Use of Opiates for Diarrhea	√	Not included
ESR	Not included	√
Albumin	Not included	√
Perirectal Disease	Not included	√

The table above is taken from the June 1, 2006 Meeting with the Sponsor.

APPENDIX 3: CDAI Scoring System

The CDAI Scoring System

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: Check all items that apply: □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/ non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil/Imodium/Loperamide /opiates for diarrhea 0 = no, 1 = yes	_____	X	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	X	10	
7. Hematocrit:[a] _____	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal ____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height[b] __ __ __ . __ (kg)	100 × [1 – (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

a. Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

b. Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

Source: Table 7 on page 157 of the M06-806 CSR.

APPENDIX 4: PCDAI Scoring System

The PCDAI Scoring System

		Score
1. Abdominal pain rating		
- None	= 0 p	
- Mild - Brief, does not interfere with activities	= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal	= 10 p	
2. Stools (per day)		
- 0 – 1 liquid stools, no blood	= 0 p	
- Up to 2 semi-formed with small blood, or 2 – 5 liquid	= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	= 10 p	
3. Patient Functioning, General Well-Being		
- No limitation of activities, well	= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par	= 5 p	
- Frequent limitation of activity, very poor	= 10 p	

LABORATORY		Score
4. HCT: Male and female ≤ 10 years:	Male 11 – 14 years:	
≥ 33 = 0 p	≥ 35 = 0 p	
28 – 32 = 2.5 p	30 – 34 = 2.5 p	
< 28 = 5 p	< 30 = 5 p	
Female 11 – 19 years: ≥ 34 = 0 p	Male 15 – 19 years: ≥ 37 = 0 p	
29 – 33 = 2.5 p	32 – 36 = 2.5 p	
< 29 = 5 p	< 32 = 5 p	
5. ESR (mm/hr) < 20 = 0 p		
20 – 50 = 2.5 p		
> 50 = 5 p		
6. Albumin (g/dL) ≥ 3.5 = 0 p		
3.1 – 3.4 = 5 p		
≤ 3.0 = 10 p		

EXAMINATION		Score
7. Weight - Weight gain or voluntary weight stable/loss	= 0 p	
- Involuntary weight stable, weight loss 1% – 9%	= 5 p	
- Weight loss ≥ 10%	= 10 p	

The PCDAI Scoring System (continued)

8. Height	At Diagnosis: Follow-up: < 1 channel decrease = 0 p Height velocity ≥ –1SD ≥ 1, < 2 channel decrease = 5 p Height velocity < –1SD, > –2SD ≥ 2 channel decrease = 10 p Height velocity ≤ –2SD	= 0 p = 5 p = 10 p	
9. Abdomen	- No tenderness, no mass - Tenderness, or mass without tenderness - Tenderness, involuntary guarding, definite mass	= 0 p = 5 p = 10 p	
10. Perirectal disease	- None, asymptomatic tags - 1 – 2 indolent fistula, scant drainage, no tenderness - Active fistula, drainage, tenderness, or abscess	= 0 p = 5 p = 10 p	
11. Extra-intestinal Manifestations (Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*) - None - One - ≥ Two		= 0 p = 5 p = 10 p	
TOTAL SCORE	**Pediatric Crohn's Disease Activity Index (PCDAI)**		

Source: Table 6 on pages 154-155 of the M06-806 CSR.

Note: SD = Standard Deviation; p = points.

APPENDIX 5: CDAI Remission Rates and PCDAI Remission Rates in Subjects ≥ 13 Years Old and Calculation of Conversion Factor (Study M06-806)

The table below shows the CDAI Remission rates and the PCDAI Remission rates for Subjects ≥ 13 years old in the Low Dose Group, the High Dose Group, and the Overall Group; also, the table shows the calculation of Conversion Factor (CF). CF = (CDAI Remission Rate) ÷ (PCDAI Remission Rate).

Table 27. Subjects ≥ 13 Years Old: CDAI Remission Rate, PCDAI Remission Rate, and Conversion Factor (Study M06-806)

TREATMENT	CDAI REMISSION (X) n/N (%)		PCDAI REMISSION (Y) n/N (%)		CONVERSION FACTOR (CF=X/Y)
ADALIMUMAB LOW DOSE	33/60	(55.0)	21/60	(35.0)	1.57
ADALIMUMAB HIGH DOSE	29/62	(46.8)	24/62	(38.7)	1.21
ADALIMUMAB OVERALL	62/122	(50.8)	45/122	(36.9)	1.38

Source: Page 676 of the M06-806 Study Report.

APPENDIX 6: External Comparisons - Applicant's Analyses of Primary Endpoint, Fourth-Ranked Secondary Endpoint, and Fifth-Ranked Secondary Endpoint.

The analyses presented below of the comparison using "adjusted PCDAI" data from this study to external data (from Study M02-404) (using CDAI) for the primary endpoint, fourth-ranked secondary endpoint, and fifth-ranked secondary endpoint are considered exploratory. See discussion in Section 7.3.6 of this CDTL Review.

Primary Endpoint

Table 28: External Comparison of the Proportion of Subjects in PCDAI Clinical Remission at Week 26 - NRI (ITT Analysis Set)

Adalimumab	N	Proportion of Subjects in Remission[a]	Difference[b]	95% CI[c]
Study M02-404 (40 mg eow [ITT])	260	33.46	--	--
Study M06-806 Low-Dose	95	44.66	11.20	-0.33, 22.73
Study M06-806 High-Dose	93	46.77	13.31	1.66, 24.96
Study M06-806 Overall	188	46.17	12.71	3.56, 21.86

CI = confidence interval; eow = every other week; ITT = intent-to-treat; NRI = non-responder imputation; PCDAI = Pediatric Crohn's Disease Activity Index

a. For Study M02-404, the proportion of subjects in remission is based on CDAI clinical remission on ITT analysis and for Study M06-806, the proportion of subjects in remission is based on the adjusted PCDAI clinical remission.

b. Difference is between Study M06-806 adalimumab dose group and Study M02-404 (40 mg eow [ITT]).

c. The CI is based on normal approximation.

CSR Table 25 pg 236

Fourth-Ranked Secondary Endpoint

Table 29 Clinical Remission at Week 26 (inWeek 4 Clinical Responders)

	M06-806		M02-404 mITT[d] Set N = 172	
	N	%	%	95% CI[e]
4. PCDAI clinical remission at Week 26 for subjects who were responders at Week 4[f]			39.53	
Overall	155	52.02		1.75, 23.22
High-Dose	75	54.00		1.03, 27.90
Low-Dose	80	49.34		-3.36, 22.98

d. mITT refers to Week 4 responders in Study M02-404 randomized to 40 mg eow.
e. The CI was based on normal approximation.
f. Adjusted PCDAI; only the percent remission was converted and compared in the external analysis.

Source: Page 248 of the M06-806 Study Report

Fifth-Ranked Secondary Endpoint

Table 30 Clinical Remission at Week 4

	M06-806 N = 192	M02-404 Overall N = 854	
5. PCDAI clinical remission at Week 4[f]	55.63	25.29	22.73, 37.95

f. Adjusted PCDAI; only the percent remission was converted and compared in the external analysis.

Source: Page 248 of the M06-806 Study Report

APPENDIX 7: SAE's in DB Maintenance Period

Table 31. Proportion of Subjects with SAE's by Descending Frequency in High-Dose Treatment Group - DB Maintenance Period (M06-806) (Safety Analysis Set)

	Adalimumab, n (%)	
	Low-Dose 20 mg or 10 mg eow N = 95	High-Dose 40 mg or 20 mg eow N = 93
Any serious adverse event	19 (20.0)	22 (23.7)
Crohn's disease	15 (15.8)	12 (12.9)
Anemia	0	4 (4.3)
Small intestinal obstruction	0	1 (1.1)
Abdominal abscess	0	1 (1.1)
Anal abscess	0	1 (1.1)
Gastroenteritis	0	1 (1.1)
H1N1 influenza	0	1 (1.1)
Histoplasmosis disseminated	0	1 (1.1)
Psychosomatic disease	0	1 (1.1)
Pancreatitis acute	1 (1.1)	0
Bartholin's abscess	1 (1.1)	0
Scarlet fever	1 (1.1)	0
Tooth abscess	1 (1.1)	0
Facial bones fracture	1 (1.1)	0

Note: A TEAE is defined as any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug.

The table above is taken from Page 366 of the M06-806 Study Report.

APPENDIX 8: AE's Leading to Discontinuation in DB Maintenance Period

Table 32. Proportion of Subjects with AE's Leading to Discontinuation - DB Maintenance Period (M06-806) (Safety Analysis Set)

	Adalimumab, n (%)	
	Low-Dose 20 mg or 10 mg Eow N = 95	High-Dose 40 mg or 20 mg Eow N = 93
Crohn's disease	10 (10.5)	11 (11.8)
Asthenia	0	1 (1.1)
Diarrhea	0	1 (1.1)
Vomiting	0	1 (1.1)
Abdominal pain upper	0	1 (1.1)
Abdominal abscess	0	1 (1.1)
Adenovirus infection	0	1 (1.1)
H1N1 infection	0	1 (1.1)
Histoplasmosis disseminated	0	1 (1.1)
Decreased appetite	0	1 (1.1)
Anal fistula	1 (1.1)	0
Injection site swelling	1 (1.1)	0
Injection site warmth	1 (1.1)	0

Note: A TEAE is defined as any AE with an onset date on or after the first DB dose and prior to the earliest time of the DB ew dose in Study M06-806, the first study drug in Study M06-807, or up to 70 days after the last dose of study drug if subject discontinued prematurely or completed the study while receiving the eow DB study drug.

The table above is taken from Page 369 of the M06-806 Study Report.

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/s/

ANIL K RAJPAL
09/19/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number	125057/356
Priority or Standard	Standard
Submit Date	29 August 2013
Received Date(s)	29 August 2013
PDUFA Goal Date	28 September 2014 (extended)
Division / Office	DGIEP / ODE 3
Reviewer Name	Marjorie Dannis, M.D.
Review Completion Date	10 August 2014
Established Name	Adalimumab
Trade Name	Humira
Therapeutic Class	TNF Antagonist
Applicant	AbbVie
Formulation(s)	10 mg/0.2mL in prefilled syringe or 20 mg/0.4mL in prefilled syringe
Dosing Regimen	*< 40 kg:* Week 0: 80 mg SC Week 2: 40 mg SC (b) (4) *≥40 kg:* Week 0: 80 mg SC Week 2: 40 mg SC (b) (4)
Indication(s)	Reducing signs and symptoms, and inducing and maintaining induction of clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease
Intended Population(s)	Pediatric patients 6 years of age and older with moderately to severely active Crohn's disease colitis who (b) (4) (b) (4)

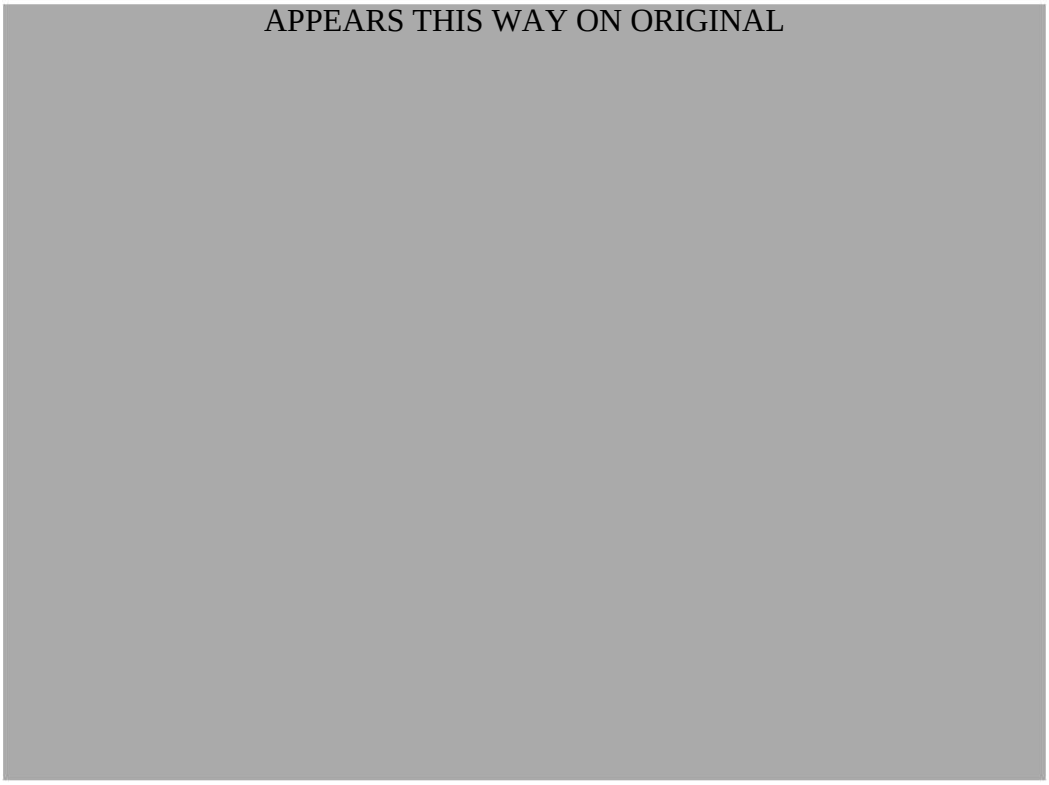
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Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for adalimumab for "reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4) (b) (4)

1.2 Risk Benefit Assessment

Review of the current application reveals that the benefit of treatment with adalimumab for reducing signs and symptoms and inducing and maintaining clinical remission in the appropriate pediatric CD population outweighs the risk of adalimumab. Adalimumab is a product with a known safety profile approved for several indications in several different disease processes (including adult CD patients with the same indication). It is recognized that CD is similar (although not identical) in adults and children.The pivotal study shows that the product is efficacious with an acceptable safety profile for a pediatric patient population who have had an inadequate response to conventional therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Adalimumab is a chimeric IgG monoclonal antibody that binds to TNFα and blocks its interaction with cell surface receptors, which in turn inhibits TNFα-induced pro-inflammatory effects. Adalimumab was originally approved for rheumatoid arthritis in

2002. Since then, it has 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 (CD), plaque psoriasis and ulcerative colitis (UC). For the adult CD indication, adalimumab is approved 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. Adalimumab 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."

2.2 Currently Available Treatments for Proposed Indications

Currently, infliximab is FDA approved for "reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have 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.

2.4 Important Safety Issues With Consideration to Related Drugs

An increased risk of serious infections and malignancies is associated with TNF antagonist therapy. These risks are adequately reflected in current labeling with a boxed warning.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant Clinical Pre-submission Regulatory Background	
Date	**Action**
February 2007	➢ Adalimumab is approved in adults with the new indication of "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; and reducing signs and symptoms an inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab" ➢ With this approval, there was a deferred pediatric study required under Pediatric Research Equity Act (PREA) which was considered a required postmarketing study commitment. ➢ The Sponsor agreed to conduct a study in pediatric patients with moderately to severely active CD. ➢ Furthermore, they agreed to complete and submit data from their required study protocol M06-806 (a one-year, multi-center, randomized, double-blind study designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in the induction and maintenance of clinical remission in pediatric subjects 6 to 17 years of age with moderate to severe Crohn's disease).
April 12, 2012	Pre BLA Meeting: ➢ The Division agreed that the PK modeling and simulation approach appeared to be adequate to support the alternative induction dosing regimen over 2 days given the half-life of adalimumab ➢ (b) (4) ➢ ➢ The Division **did not agree** that the "external comparison" would provide sufficient evidence for judging the efficacy of adalimumab in this population and further stated that these types of analyses were considered exploratory and have no statistical or inferential value.
December 2012	Sponsor requests a deferral extension for the PMC that was established under PREA which had an Original Final Report Submission Date of April 30, 2011. Difficulties in enrolling pediatric patients into the study was the reason stated for the delay.

(b) (4)

Relevant Clinical Pre-submission Regulatory Background	
Date	**Action**
June 2013	Sponsor's request is granted and the New Final Report Submission Date: becomes December 31, 2013.
August 2013	sBLA submitted

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was acceptable, although the pivotal study was not placed in the appropriate location. For the efficacy analyses, the Sponsor could have presented the data in a more organized manner. A better distinction between "internal analyses" and "external analyses" would have been beneficial. Clearer summary tables which included the most relevant endpoints should have been provided. Nonetheless, the Sponsor was responsive to the Division's several requests for information and provided the requested information in a timely manner.

3.2 Compliance with Good Clinical Practices

The Sponsor certified that all of the studies contained in the BLA submission were performed in compliance with guidelines for Good Clinical Practice (GCP) and were conducted under the supervision of an IRB, or IEC equivalent, with adequate informed consent procedures.

3.3 Financial Disclosures

In the submission, the Sponsor 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 five investigators involved in Study M06-806 and/or Study M06-807. Four of the five investigators had received significant payments having total value in excess of $25,000 from the Sponsor, other than payments for conducting this clinical study. One investigator had a spouse who became employed by Abbott Laboratories in 2009 and according to his financial disclosure he has "significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the

Sponsor of the covered study" This reviewer does not believe these disclosures had an effect on overall study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

To support the dosing of this indication, a newly developed 10 mg PFS was introduced in this supplement. The formulation and container closure of the drug product in the proposed 10 mg/0.2mL PFS presentation was identical to the approved Humira presentations. There was also updated information provided for the anti-drug antibody assay. In addition, the Sponsor made a change in the confirmatory ADA assay.

According to CMC Reviewer, Jun Park, Ph.D, from a CMC perspective, the application was recommended for approval. See complete CMC Review dated 2 June 2014 for further details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this supplemental BLA.

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4.4 Clinical Pharmacology

According to the Office of Clinical Pharmacology, Divisions of Pharmacometrics (OCP/DPM) and Clinical Pharmacology 3 (OCP/DCP 3) the data were acceptable for supporting the approval of adalimumab for the treatment of pediatrics patients 6 years and older with Crohn's disease with the following dose recommendations:

Body Weight	Induction Phase	Maintenance Phase
≥ 40 kg	160 mg at Week 0 followed by 80 mg at Week 2	40 mg every other week (EOW)
< 40 kg	80 mg at week 0 followed by 40 mg at week 2	20 mg EOW

Furthermore, the Clinical Pharmacology Review dated 21 August 2014 stated:

"The exposure-response relationship between trough concentrations at Week 26 and clinical remission based on unadjusted PCDAI at Week 26 showed that High Dose group achieved similar trough concentrations as those in adults and achieved greater clinical remission than the Low Dose group. This is consistent with results observed with dose response for clinical remission at week 26. There was trend in dose response showing that higher dose provided numerically higher benefit for other secondary endpoints (clinical remission at Week 52, clinical response at Week 26, and clinical response at Week 52). When clinical remission was evaluated over time, high dose consistently showed higher benefit than low dose during the maintenance.
Low Dose (20 mg EOW in patients with body weight ≥ 40 kg and 10 mg EOW in patients with body weight < 40 kg) produced lower levels of concentrations of adalimumab which led to lower rate of clinical remission at Week 26 and Week 52 when compared to High Dose. Furthermore, concentrations following low doses are lower than concentrations observed with 40 mg EOW in adults. Trough concentrations and clinical remission at Week 26 following High Dose (40 mg EOW in patients with body weight ≥ 40 kg and 20 mg EOW in patients with body weight < 40 kg) were comparable with those in adults following 40 mg EOW dosing regimen. In addition, a higher proportion of patients in the low dose group got dose escalated due to a disease flare or inadequate response compared to the high dose group. Therefore, High Dose is recommended for the maintenance phase."

4.4.1 Mechanism of Action

Current Adalimumab Label:
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 Adalimumab Label:
After treatment with adalimumab, 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 levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

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4.4.3 Pharmacokinetics

Current Adalimumab Label:
In pediatric subjects with CD weighing ≥ 40 kg, the mean ±SD serum adalimumab concentrations were 15.7±(b) (4) mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were10.5±6.0 mcg/mL at Week 52 following subcutaneous doses of 40 mg every other week. In pediatric subjects with CD weighing < 40 kg, the mean ±SD serum adalimumab concentrations were 10.6±6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean ±SD steady-state trough serum adalimumab concentrations were 6.9±3.6 mcg/mL at Week 52 following subcutaneous doses of 20 mg every other week.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Description of Clinical Efficacy/Safety Study (Pivotal)

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M06-806/ 45/ BEL, CAN, CZ, FR, IT, NL, POL, UK, US/ 52 weeks	04 May 2007 Completed 18 May 2010 192 subjects	Randomized, DB, 2 dose regimens, OL induction, DB period with possible OL period	Adalimumab SC injection, OL induction: 160 mg at Wk 0 and 80 mg at Wk 2 (BW ≥ 40 kg); or 80 mg at Wk 0 and 40 mg at Wk 2 (BW < 40 kg) DB maintenance: randomized to LD eow or HD eow at Wk 4: LD = 10 mg (BW < 40 kg) or 20 mg (BW ≥ 40 kg); HD = 20 mg (BW < 40 kg) or 40 mg (BW ≥ 40 kg) eow, from Wk 12 option to increase to ew, then OL HD if flare	Safety, efficacy and PK of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD	LD 95/58, HD 93/66 (a total of 192 entered/ 124 completed)[a]	105/83 14 yr (6 – 17 yr)	Moderate to severe CD, failed conventional therapy for CD or lost response/had intolerance to infliximab	clinical remission (PCDAI score ≤ 10) at Wk 26; external efficacy comparisons with adult Study M02-404; internal comparison HD vs. LD

a. Of the 192 subjects who entered the study, 4 subjects dropped out during the open-label induction period and were not randomized in Study M06-806.

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Table 2: Description of Clinical Efficacy and Safety Studies (Supportive)

Study ID/ No. of Centers/ Locations/ Duration	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Efficacy Endpoints
M06-807/ 31 sites/ BEL, CAN, CZ, POL, UK, US/ 5 years	01 May 2008/ Ongoing, 31 July 2011	OL extension study of Study M06-806	Adalimumab SC injection 40 mg eow (BW ≥ 40 kg) or 20 mg eow (BW < 40 kg) or OL dose in M06-806 (40 mg ew or 20 mg ew); from Wk 8 option to increase to ew if flare	Long-term safety and efficacy (maintenance of clinical response)	100 entered/ 0 completed to date/ 73 ongoing 100 analyzed for interim analysis	52/48, 14 years (7 – 17 years)	Moderate to severe CD, successful completion of Study M06-806 through Week 52, responder at any time point during Study M06-806 (defined as having achieved at least a 15-point reduction in PCDAI from Baseline)	Maintenance of PCDAI clinical response (PCDAI score ≥ 15 points lower than the Study M06-806 Baseline score)

SCS Table 2 pg 9

5.2 Review Strategy

For this submission, pivotal study M06-806 was 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). The extension study M06-807 listed above is currently ongoing and specific aspects are discussed when relevant.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title
Study M06-806
A Multicenter, Double-blind Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease

Study Centers and Study Period
Study M06-806
This study was conducted from 04 May 2007 to 18 May 2010 in 45 sites in Belgium, Canada, Czech Republic, France, Italy, The Netherlands, Poland, the United Kingdom, and the United States.

Study Objectives
The objective of the study was to demonstrate the safety and efficacy of adalimumab for the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD and to assess the pharmacokinetics (PK) of adalimumab administered by subcutaneous (SC) injection.

Study Design
This study was a multi-center, randomized, double-blind, safety, efficacy and PK study designed to demonstrate the effectiveness of two dosage regimens of adalimumab in the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD. This study contained two dosing periods, a 4-week open-label induction period, and a 48-week double-blind period. Subjects who experienced a flare or non−response following an 8-week course of double-blinded weekly therapy could be switched to open label weekly therapy. See Figure 1 below.

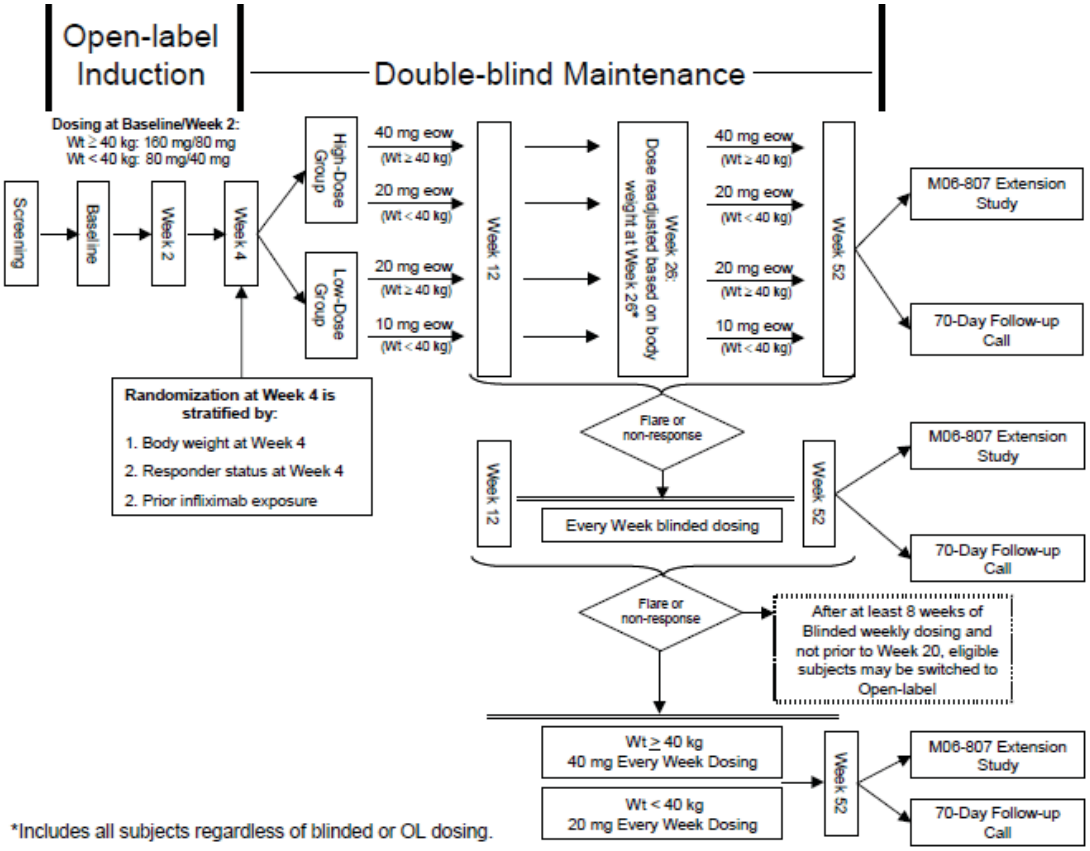
Approximately 180 pediatric subjects between the ages of 6 and 17, inclusive, with a diagnosis of moderate to severe CD (defined by a PCDAI > 30) who had failed conventional therapy for CD (as defined in the Inclusion Criteria) or who have previously lost response or had adverse reactions to infliximab and with confirmation of CD by endoscopic or radiological evaluation, were enrolled at approximately 50 sites in the United States, Canada, and Europe. Enrollment was dependent on meeting all inclusion and none of the exclusion criteria. At least 80 subjects were ≥ 13 years old at Baseline and one-third to one −half of the study population were subjects who had previously lost response or had adverse reactions to infliximab.

The open-label induction dose was dependent on the subject's Baseline body weight. If a subject was ≥ 40 kg, they received 160 mg and then 80 mg adalimumab at Weeks 0 and 2, respectively. If a subject was < 40 kg, they received 80 mg and then 40 mg at Weeks 0 and 2, respectively. At Week 4, subjects were stratified according to their Week 4 body weight, Week 4 responder status (clinical response was defined as PCDAI decrease ≥ 15 points from the Baseline score), and their prior exposure to infliximab, and randomized 1:1 to one of two maintenance treatment groups. One dose cohort received either 40 mg adalimumab SC (if BW ≥ 40 kg) or 20 mg adalimumab SC (if BW < 40 kg) per dose every other day (eow), while the other dose cohort received either 20 mg adalimumab SC (if BW ≥ 40 kg) or 10 mg adalimumab SC (if BW < 40 kg) per dose eow. Subject body weight taken at Week 26 was used to readjust the maintenance dosing regimen for subjects whose body weight had increased from < 40 kg to ≥ 40 kg during the study.

The duration of the study was up to 65 weeks, which included a 1-week to 3-week Screening period, an OL Induction period, a Maintenance period, and a 70-day follow-up phone call for all subjects who either terminated early from the study or did not rollover into the extension study (Study M06-807).

In addition to the PCDAI, the Crohn's Disease Activity Index (CDAI) was applied to subjects ≥ 13 years of age. Additional efficacy assessments, as well as safety and PK measurements were performed throughout the study.

Figure 1: Study Design



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Efficacy Measurements

Study procedures were performed as summarized in the study schematic presented in Table 3 below.

Table 3: Study Assessments

Activity	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26	Week 32	Week 40	Week 48	Week 52/ Early Term	Unscheduled Visit	70-Day Follow-up Phone Call
Inclusion/exclusion criteria	X	X													
Informed consent	X														
Medical/surgical history (including CD surgical/ medical history)	X	X													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PPD skin test[a]	X														
Chest x-ray[b]	X								X						
Electrocardiogram[c]	X														
Serum pregnancy tests[d]	X														
Urine pregnancy test[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C. difficile	X														
General laboratory assessments[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Activity	Screening	Baseline	Week2	Week4	Week8	Week12	Week16	Week20	Week26	Week32	Week40	Week48	Week 52/ Early Term	Unscheduled Visit	70-Day Follow-up Phone Call
Urinalysis[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	
PK blood sample		X	X	X			X		X				X		
Anti-adalimumab blood levels		X					X		X				X		
Human anti-chimeric antibody to infliximab/infliximab levels[h]		X													
Erythrocyte sedimentation rate		X	X	X	X	X	X	X	X	X	X	X	X	X	
C-reactive protein		X		X					X				X		
Anti-nuclear antibodies		X			X								X		
Anti-dsDNA[i]		X			X								X		
PCDAI		X	X	X	X	X	X	X	X	X	X	X	X	X	
CDAI[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III Questionnaire		X				X			X				X		
HCRU		X	X	X	X	X	X	X	X	X	X	X	X		

Activity	Screen-ing	Base-line	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26	Week 32	Week 40	Week 48	Week 52/ Early Term	Unsched-uled Visit	70-Day Follow-up Phone Call
Work Productivity and Impairment Questionnaire: CD		X	X	X	X	X	X	X	X	X	X	X	X		
X-ray for bone age	X												X		
Serum bone markers[k]		X							X				X		
Anthropometric evaluations[l]		X							X				X		
Corticosteroid [m]				X	X	X	X	X	X	X	X	X		X	
Immunosuppressant discontinuation[n]									X	X	X	X		X	
Adverse events[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense adalimumab		X	X	X	X	X	X	X	X	X	X	X		X[p]	

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; ds-DNA = double-stranded-DNA; HCRU = Healthcare Resource Utilization; PCDAI = Pediatric Crohn's Disease Activity Index; PK = pharmacokinetics; PPD = purified protein derivative

a. Was to be read by the investigator or a qualified delegate during the period between 48 and 72 hours after injection. If a subject had a PPD test within 3 months, the test did not need to be repeated provided all protocol required documentation were available. These cases were to be discussed with the Medical Monitor.

b. Included a posteroanterior (PA) and lateral view. Week 26 CXR was required only if PPD was positive at Screening. If a subject had a CXR performed within 3 months, the test did not need to be repeated provided all protocol required documentation was available. These cases were to be discussed with the Medical Monitor.

c. If a subject had an ECG within 3 months, and all protocol required documentation was available, this test did not need to be repeated. These cases were to be discussed with the Medical Monitor.

d. To be performed on all females of child-bearing potential. Serum test at Screening. Urine test at Baseline and at all subsequent study visits.

e. Vital sign determinations of height, weight, sitting BP, heart rate, respiratory rate, and body temperature were to be obtained at each visit.

f. Blood draws were to be performed after questionnaire and vital signs determinations and before adalimumab administration.

g. Microscopic urinalysis performed at Screening and at any other visits if dipstick UA was abnormal (protein greater than a trace, blood greater than 5 to 10 Ery/µL, moderate or large ketone count or glucose greater than 50 mg/dL.

h. HACA and infliximab samples were to be collected on all subjects.

i. Anti-dsDNA performed automatically if anti-nuclear antibody (ANA) result was positive.

j. For subjects who were age 13 and older at time of Baseline, a PCDAI and a CDAI were to be completed at each visit.

k. Osteocalcin, bone specific alkaline phosphatase, N-telopeptide.

l. Body mass index (BMI) and z-score for height were to be calculated by Abbott based on vital sign measurements for weight and height.

m. Subjects were to begin a taper if qualifications were met at Week 4 or at subsequent study visits if the subject met the clinical response criterion.

n. IMM therapy could be discontinued at Week 26 or at subsequent study visits at the investigator's discretion if the subject met the clinical response criterion.

o. All SAEs were to be captured from the time that the subject signed the ICF throughout the trial.

p. Medication could be dispensed at the visit if the reason for the unscheduled visit was to change the frequency of adalimumab administration from blinded eow to blinded ew.

CSR Table 1 pg 30-33

In the study, The Crohn's Disease Activity Index (CDAI) and the Pediatric Crohn's Disease Activity Index (PCDAI) were both utilized as tools to measure disease activity, the PCDAI exclusively for patients <13 years of age and both tools for patients age 13 or older. Tables 4 and 5 below describe the details of both indices.

Table 4: PCDAI Assessments and Score Calculation

		Score
1. Abdominal pain rating		
- None	= 0 p	
- Mild - Brief, does not interfere with activities	= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal	= 10 p	
2. Stools (per day)		
- 0 – 1 liquid stools, no blood	= 0 p	
- Up to 2 semi-formed with small blood, or 2 – 5 liquid	= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	= 10 p	
3. Patient Functioning, General Well-Being		
- No limitation of activities, well	= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par	= 5 p	
- Frequent limitation of activity, very poor	= 10 p	
LABORATORY		**Score**
4. HCT: Male and female ≤ 10 years: ≥ 33 = 0 p; 28 – 32 = 2.5 p; < 28 = 5 p	Male 11 – 14 years: ≥ 35 = 0 p; 30 – 34 = 2.5 p; < 30 = 5 p	
Female 11 – 19 years: ≥ 34 = 0 p; 29 – 33 = 2.5 p; < 29 = 5 p	Male 15 – 19 years: ≥ 37 = 0 p; 32 – 36 = 2.5 p; < 32 = 5 p	
5. ESR (mm/hr) < 20 = 0 p; 20 – 50 = 2.5 p; > 50 = 5 p		
6. Albumin (g/dL) ≥ 3.5 = 0 p; 3.1 – 3.4 = 5 p; ≤ 3.0 = 10 p		
EXAMINATION		**Score**
7. Weight - Weight gain or voluntary weight stable/loss	= 0 p	
- Involuntary weight stable, weight loss 1% – 9%	= 5 p	
- Weight loss ≥ 10%	= 10 p	

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Table 5: CDAI Assessments and Score Calculation

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: Check all items that apply: □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/ non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil/Imodium/Loperamide /opiates for diarrhea 0 = no, 1 = yes	_____	X	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	X	10	
7. Hematocrit:[a] _____	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal ____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height[b] __ __ __ . __ (kg)	100 × [1 – (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

a. Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

b. Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

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Of note, at this time, DGIEP is exploring other tools which could better quantify disease activity. However, the PCDAI and CDAI have been used to help determine efficacy is previous registration trials.

Study Population

Key Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

- 6-17 years old inclusive, prior to Baseline dosing
- Subjects with a diagnosis of CD for greater than 12 weeks prior to Screening, confirmed by endoscopy or radiologic evaluation

- PCDAI > 30 despite concurrent treatment with an oral corticosteroid, and/or azathioprine (AZA) or 6-mercaptopurine (6-MP), or methotrexate (MTX) defined by specific criteria
- If female of childbearing potential must use an approved form of contraception throughout the entire study period and for 150 days after
- Subjects who had previously received infliximab must have had an initial response and then discontinued use due to a loss of response or must have discontinued use due to intolerance to the medication[2]

Key Exclusion Criteria

Patients who met any of the following criteria were excluded from the study (see Appendix A for complete list of exclusion criteria)

- History of cancer or lymphoproliferative disease other than a successfully and completely treated cutaneous squamous cell or basal cell carcinoma or carcinoma–in-situ of the cervix.
- History of listeria, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus (HIV) infection, any immunodeficiency syndrome, central nervous system (CNS) demyelinating disease or active tuberculosis (TB) or severe infection
- Subject with a current diagnosis of ulcerative colitis or indeterminate colitis as determined by the investigator and Medical Monitor
- Subject with symptomatic known obstructive strictures
- Subject who had surgical bowel resections within the past 24 weeks of the Baseline visit or planned any resection at any time point while enrolled in the study
- Subject with an ostomy or ileo-anal pouch. (Subjects with a previous ileo-rectal anastomosis were not excluded.)
- Subject who had short bowel syndrome as determined by the investigator
- Subject who was currently receiving total parenteral nutrition
- Subject who had received any investigational chemical agent in the past 30 days or 5 half-lives prior to Baseline (whichever was longer)
- Subject who had received any investigational biological agent in the past 16 weeks or 5 half-lives prior to Baseline (whichever was longer)
- Subject who had systemic antibiotic, antiviral, or antifungal treatment(s) within 3 weeks prior to Baseline for any non-CD-related infections
- Subjects with positive C. difficile stool assay
- Subject who previously used infliximab within 8 weeks of Baseline.
- Subject who previously used infliximab and had not clinically responded at any time ("primary non-responder") unless subject experienced a treatment limiting reaction to infliximab.
- Previous treatment with any other anti-TNF agent except infliximab.

[2] See Appendix D for definitions of “loss of response” and “intolerance”

Study Treatments
All subjects were to receive an induction regimen administered at Baseline and Week 2. The OL induction dose was dependent on the subject's Baseline BW. If a subject was ≥ 40 kg, they were to receive 160 mg and then 80 mg adalimumab at Weeks 0 and 2, respectively. If a subject was < 40 kg, they were to receive 80 mg and then 40 mg at Weeks 0 and 2, respectively.

At Week 4, subjects were to be stratified according to Week 4 BW, Week 4 responder status (clinical response was defined as PCDAI decrease ≥ 15 points from the Baseline score), and prior exposure to infliximab, and randomized 1:1 to one of two maintenance treatment groups (Low-Dose or High-dose).

Subjects randomized to the High-Dose treatment group were to receive either 40 mg adalimumab SC eow (if Week 4 BW ≥ 40 kg) or 20 mg adalimumab SC eow (if Week 4 BW < 40 kg).

Subjects randomized to the Low-Dose treatment group were to receive either 20 mg adalimumab SC eow (if Week 4 BW ≥ 40 kg) or 10 mg adalimumab SC eow (if Week 4 BW < 40 kg).

Subject body weight (BW) taken at Week 26 was to be used to readjust the maintenance dosing regimen for subjects whose BW had increased from < 40 kg to ≥ 40 kg during the study.

Subjects were expected to remain on blinded eow therapy throughout the 48-week study period. However, starting at the Week 12 study visit, subjects who experienced a disease flare (increase in the PCDAI of ≥ 15 points when compared to Week 4 and an absolute PCDAI above 30) **or were non-responders** (not achieving a decrease in the PCDAI score of at least 15 points when compared to the Baseline score for 2 consecutive visits at least 2 weeks apart), **could be switched from blinded eow dosing to blinded ew dosing, continuing with the same blinded dose**. If disease activity was of such severity that new interventions with prohibited medications were indicated in the judgment of the investigator, the subject was to be terminated from the study.

During blinded ew treatment, if a subject continued to experience a flare or met the definition of non-response following an 8-week course of DB ew therapy, they were to be switched to OL ew therapy. The dosage of the OL ew therapy was 20 mg for subjects < 40 kg and 40 mg for subjects ≥ 40 kg.

Concomitant Therapy

Subjects must continue their doses of azathioprine, 6-MP, and MTX provided they are on these medications for at least eight weeks prior to Baseline and their doses have been stable for at least four weeks prior to Baseline. Doses are to remain stable throughout the study. Subjects must continue doses of aminosalicylates, or Crohn's-related antibiotics (fluoroquinolones such as ciprofloxacin, nitroimidazole derivatives such as metronidazole) provided they have been on stable doses of these medications for at least 4 weeks prior to Baseline. Doses of these medications are to remain stable throughout the study.

Subjects must continue their doses of growth hormone provided they are on a stable dose 12 weeks prior to Baseline. Doses of growth hormone are to remain stable throughout the study. Reductions in concomitant therapy will be allowed for Crohn's treatment-related toxicities assessed as moderate to severe in the opinion of the investigator.

Prednisone ≤ 40 mg/day (or equivalent) is permitted provided subjects are on stable (± 5 mg) doses for at least two weeks prior to Baseline.

Budesonide ≤ 9 mg/day is permitted provided subjects are on stable doses for at least two weeks prior to Baseline.

Subjects may not be on both budesonide and prednisone (or equivalent) simultaneously.

Starting at Week 4, subjects who are on corticosteroid and are responders must taper the corticosteroid as below:

Corticosteroid Taper
Starting at Week 4, subjects who meet the definition of clinical response (defined as a PCDAI decrease of ≥ 15 points compared to Baseline) must begin a corticosteroid taper according to the following schedule:

Tapering Schedule	Dose	Rate
Prednisone (or equivalent)	> 10 mg	5 mg/week
	≤ 10 mg	2.5 mg/week
Budesonide	≤ 9 mg	3 mg/week

Study Visits and Procedures
The study visits and related safety assessments are summarized in Table 3 above.

Study Endpoints

Primary Variables
The primary efficacy endpoint was to be **the proportion of subjects who were in clinical remission at Week 26,** as measured by the PCDAI in the intent-to-treat (ITT) population**. PCDAI clinical remission was defined as PCDAI score ≤ 10**.

Secondary Variables
There was an extensive list of secondary efficacy variables that was analyzed by the Sponsor. Comparisons were made between Low-Dose and High-Dose treatment groups. This review will focus on the first several secondary endpoints, numbers 1-3, (numbers 1-8 are hierarchically ordered) which are the most clinically relevant.[3] Of note, since these are ranked secondary endpoints, the primary endpoint must be met (statistical significance) for the secondary endpoints to be considered significant. Furthermore, each prior secondary endpoint must be met in order for the next ranked endpoint to be significant.

In addition, for some analyses, the Sponsor did an "external comparison" between the results of the adult pivotal study for CD (M02-404) and the results of this pediatric study. These "external comparisons" were considered exploratory[4] but will be briefly mentioned in Section 6.1.10.

1. Proportion of subjects in PCDAI clinical remission at Week 52.
2. Proportion of subjects in PCDAI clinical response at Week 26.
3. Proportion of subjects in PCDAI clinical response at Week 52.
4. Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders, for *external comparison* with modified ITT data from adult Study M02-404.
5. PCDAI clinical remission at Week 4, for *external comparison* with OL induction at Week 4 for all subjects in adult Study M02-404.
6. Proportion of subjects receiving corticosteroids at Baseline who have discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and are in PCDAI clinical remission at Week 26.
7. Change from Baseline in "z-score" for height velocity at Week 26.
8. Change from Baseline in total IMPACT III scores at Week 26. Proportion of subjects in PCDAI clinical remission over time.

6 Review of Efficacy

[3] The additional list of secondary endpoints can be found in Appendix B
[4] See Section 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

6.1 Indication

The Sponsor proposed to expand the current indication in adult CD patients to pediatric CD patients. The proposed indication statement is the following:

"Adalimumab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who [redacted] (b) (4)

6.1.1 Methods

Section 5.3 contains a discussion of the pivotal study protocol. Section 6 contains the study results as well as a discussion of the efficacy issues that arose during the review of this application. The efficacy of adalimumab for the induction and maintenance of clinical remission for children ages 6-17 years old with moderately to severely active CD was partially extrapolated from the adult maintenance trial[5]. Thus, to establish efficacy in the pediatric population, only one dose-ranging, PK, efficacy (safety trial) was required. Study M06-806 was a randomized, double-blind (DB) induction and maintenance study.

Analysis Populations
Table 6 below depicts the number of patients included in each analysis population.

Table 6: Number of Patients per Analysis Set

	Induction Phase	Maintenance Phase		
Analysis Set	**N**	**Low Dose (10mg or 20 mg) eow**	**High Dose (20mg or 40 mg) eow**	**All**
ITT	188	95	93	188
PP	178	91	87	178
Safety	192	95	93	192*

***Four patients not randomized to maintenance period**
Adapted from CSR Table 10 pg 45

Table 7 below compares the number of patients who had a dose change in the Low Dose treatment group with those who had a dose change in the High Dose treatment group. There were more dose changes in the Low Dose group.

[5] Study M02-404 was the pivotal maintenance study performed in adults (who were either naïve to anti-TNF treatment or had previous experience with anti-TNF agents).

Table 7: Dose Changes During Maintenance Period (Safety Population)

	Number of Patients (%)		
	Low Dose (10mg or 20 mg) eow	High Dose (20mg or 40 mg) eow	All
Dose Change	**N=95**	**N=93**	**N=188**
Switch to every week (ew)	48 (50.5)	35 (37.6)	83 (44.1)
Switch to open label (OL)	17 (17.9)	11 (11.8)	28 (14.9)
Dose re-adjustment at Week 26	2 (2.1)	2 (2.2)	4 (2.1)

Adapted from CSR Table 11 pg 46

Efficacy Discussion

This pivotal study was designed to show whether there was a statistically significant difference in efficacy between adalimumab at a high dose and at a low dose. For the primary endpoint of clinical remission at 26 weeks, there was not a statistically significant difference between the High dose and Low dose. In addition, the first several hierarchically ordered secondary endpoints did not show a statistically significant difference between the two doses. However, there appeared to be a trend present in most of these endpoints that showed that the High Dose remission and response rates were numerically higher than the Low Dose rates. According to the Clinical Pharmacology Review:

"When clinical remission was evaluated over time, high dose consistently showed higher benefit than low dose during the maintenance. Low Dose (20 mg EOW in patients with body weight ≥ 40 kg and 10 mg EOW in patients with body weight < 40 kg) produced lower levels of concentrations of adalimumab which led to lower rate of clinical remission at Week 26 and Week 52 when compared to High Dose. Furthermore, concentrations following low doses are lower than concentrations observed with 40 mg EOW in adults. Trough concentrations and clinical remission at Week 26 following High Dose (40 mg EOW in patients with body weight ≥ 40 kg and 20 mg EOW in patients with body weight < 40 kg) were comparable with those in adults following 40 mg EOW dosing regimen"

Therefore, given that the efficacy of pediatric CD is partially extrapolated from the efficacy of adult CD, it is reasonable to choose the higher dose in this particular circumstance based upon the comments above.[6]

In addition, patients who lost response were allowed to dose escalate during the maintenance phase of the study from eow to ew dosing. Although, more patients in the Low Dose group escalated to ew dosing, these maintenance results were confounded by the lack of re-randomization at Week 12. Furthermore, the study was not designed

[6] However, in general, the lowest effective dose is typically chosen if an adequate and well controlled trial shows that there is no statistically significant difference between the doses that are studied.

appropriately to distinguish the difference in efficacy between an eow and ew dosing regimen.

6.1.2 Demographics and Baseline Disease Activity

Demographic characteristics at Baseline for all subjects in the ITT analysis set are provided below in Table 8. The majority of subjects were male (56%), white (88%), and ≥ 13 years old (65%). These demographic characteristics were similar between the treatment groups.

Table 8: Demographics Characteristics (ITT analysis set)

Demographic Subgroup	Low Dose 10mg or 20 mg N=95 eow	High Dose 20mg or 40 mg N=93 eow	All N=188
Sex (n,%)			
Male	54 (57)	51 (55)	105 (56)
Female	41 (43)	42 (45)	83 (44)
Age (years)			
median	14	14	14
Min, Max	6, 17	7, 17	6, 17
< 13 years	35 (37)	31 (33)	66 (35)
≥ 13 years	60 (63)	62 (67)	122 (65)
Race (n,%)			
Caucasian	85 (90)	81 (87)	166 (88)
Black	6 (6)	5 (5)	11 (6)
Hispanic	1 (1)	1 (1)	2 (1)
Asian	0	3 (3)	3 (2)
Other	2 (2)	3 (3)	5 (3)
Weight (kg)			
median	43	44	43
Min, Max	(19, 81)	(19, 120)	(19, 120)
< 40 kg	35 (37)	32 (34)	67 (36)
≥ 40 kg	60 (63)	61 (66)	121 (64)

Adapted from CSR, Table 12 pg 211-212

Mean Baseline PCDAI score, CRP, and ESR were similar between the treatment groups. However, it appeared that the High Dose treatment group had a numerically higher CDAI score[7] at Baseline than the Low Dose treatment group. See below in Table 9.

[7] CDAI scores only for subjects ≥ 13 years old

Table 9: Baseline Disease Activity

Demographic Subgroup	Low Dose 10mg or 20 mg N=95 eow	High Dose 20mg or 40 mg N=93 eow	All N=188
PCDAI score			
median	40	40	40
Min, Max	30, 63	25, 63	25, 63
CDAI score*			
mean	243	279	262
median	246	264	255
Min, Max	80, 432	75, 470	75, 470
C-reactive protein (CRP)			
median	1	1	1
Min, Max	0, 12	0, 17	0, 17
Erythrocyte Sedimentation Rate (ESR)			
median	28	30	29
Min, Max	1, 86	1, 135	1, 135

P value for difference was 0.024
Adapted from SCE, Table 5 pg 27

Immunomodulatory Medications (IMM), Systemic Corticosteroid, and Infliximab Use

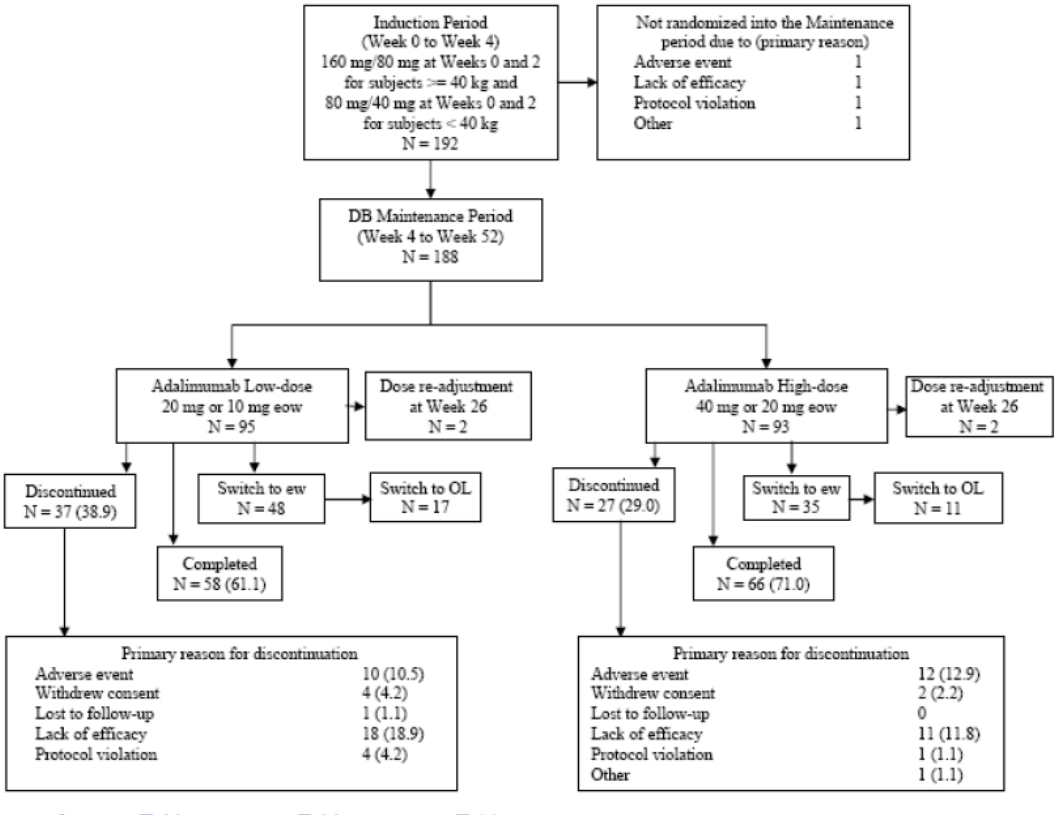
No difference was observed between treatment groups for history of infliximab use; approximately 44% of subjects had used infliximab previously. Between treatment groups, concomitant immunomodulators (IMM)[8] and systemic corticosteroid use at Baseline was numerically similar; 62% of all subjects reported IMM use at Baseline and 38% of all subjects reported systemic corticosteroid use at Baseline.[9]

[8] azathioprine, mercaptopurine, or methotrexate
[9] From SCE Tables 6 and 7 pg 28-9 see Appendix C

6.1.3 Subject Disposition

Subjects were enrolled at 45 investigative sites in the US, Canada, and Europe, with the number of subjects entered at each site ranging from 1 to 20. A total of 192 subjects received at least one dose of adalimumab and participated in the 4-week OL induction period of the study. Of these, 188 subjects participated in the DB Maintenance period. A greater proportion of subjects in the High-Dose treatment group (71%) who entered the Maintenance period completed the study compared to the proportion of subjects in the Low-Dose treatment group (61%). See Figure 2 below.

Figure 2: Disposition of Subjects



CSR Figure 2 pg 205

Disposition of subjects who completed Week 26 and Week 52 by dose regimens at the time of the visit is presented below in Table10. Among subjects who completed Week 26, a greater proportion of subjects in the High-Dose treatment group were on DB eow at Week 26 compared to the proportion of subjects in the Low-Dose treatment groups. A greater proportion of subjects completed Week 26 on OL ew in the Low-Dose treatment group compared to the High-Dose group. Among subjects who completed Week 52, a greater proportion of subjects in the High-Dose group were on DB eow compared to the Low-Dose group. A greater proportion of subjects

in the Low-Dose group who completed Week 52 were on OL ew adalimumab compared to the High-Dose group.

Table 10: Number (%) of Subjects Who Completed Weeks 26 and 52 (ITT Analysis Set)

Completed Visit Treatment	N/n (%) of Subjects	
	Low-Dose Adalimumab 20 mg or 10 mg eow	High-Dose Adalimumab 40 mg or 20 mg eow
Week 26	N = 77	N = 75
on DB eow	49 (63.6)	55 (73.3)
on DB ew	19 (24.7)	17 (22.7)
on OL ew	9 (11.7)	3 (4.0)
Week 52[a]	N = 58	N = 66
on DB eow	30 (51.7)	41 (62.1)
on DB ew	16 (27.6)	18 (27.3)
on OL ew	12 (20.7)	7 (10.6)

DB = double-blind; eow = every other week; ew = every week; ITT = intent-to-treat; OL = open-label

a. Two subjects who completed Week 52 were dosed only up to Week 48.

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6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the proportion of subjects who were in clinical remission (PCDAI score ≤ 10) at Week 26.Comparison of the primary endpoint between the Low-Dose and the High-Dose treatment groups (ITT analysis set) demonstrated that **there was no statistically significant difference between the two treatment doses (*P* = 0.075).** However, a numerically greater proportion of subjects in the High-Dose treatment group achieved PCDAI clinical remission at Week 26 as compared with the Low-Dose treatment group. See Table 11 below.

Table 11: Primary Endpoint of Week 26 Clinical Remission

	Low Maintenance Dose* 20mg /10mg eow N = 95 n/N (%)	High Maintenance Dose# 40mg / 20 mg eow N = 93	Treatment Difference (95% CI)	p-value
All	27/95 (28.4)	36/93 (38.7)	10.3 (-3.1, 23.7)	0.075

*Low Maintenance Dose 10 mg (for patients weighing < 40 kg) and 20 mg (for patients weighing ≥ 40 kg).
#High Maintenance Dose: 20 mg every other week (for patients weighing < 40 kg) and 40 mg (for patients weighing ≥ 40 kg).
Adapted from Sponsor's response to IR July 31, 2014

6.1.5 Analysis of Secondary Endpoints(s)

Discussion of the First Four hierarchically Ranked Secondary Endpoints
Comparison between treatment groups (Low- Dose vs High-Dose) of the proportion of subjects in PCDAI clinical remission at Week 52 , the proportion of subjects in PCDAI clinical response at Week 26 and the proportion of subjects in PCDAI clinical response at Week 52 did not show a statistically significant difference. However, there was a numerically higher proportion of subjects meeting each of these endpoints in the High-Dose treatment group. See Table 12 below.

Table 12: First Three Ranked Secondary Endpoints

	Low Maintenance Dose (20 or 10 mg every other week) N = 95	High Maintenance Dose (40 or 20 mg every other week) N = 93	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Response§	48%	59%	11 (-4, 25)	0.073
Week 52				
Clinical Remission‡	23%	33%	10 (-3, 23)	0.100
Clinical Response§	28%	42%	14 (0, 27)	0.038

‡ Clinical remission defined as PCDAI ≤ 10
§ Clinical response defined as reduction in PCDAI of at least 15 points from baseline
Adapted from Sponsor's response to IR July 31, 2014

In addition, although the proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders was numerically greater in the High-Dose as compared to the Low-Dose group, this difference was not statistically significant. See Table 13 below.

Table 13: Summary of Subjects in Clinical Remission at Week 26 Who Were Also Week 4 Clinical Responders by Treatment Group

	Low Maintenance Dose[a] (20 or 10 mg every other week) n/N (%)	High Maintenance Dose[b] (40 or 20 mg every other week) n/N (%)	Treatment Difference (95% CI)	p-value
Week 26				
Clinical Remission at Week 26 (in Week 4 Clinical Responders)[c,d]	25/80 (31.3)	33/75 (44.0)	12.75 (–2.39, 27.89)	0.101

a. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. Clinical remission defined as PCDAI ≤ 10.
d. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.
Sponsor's response to IR July 31, 2014

As displayed in the summary Table 14 below, all comparisons (except the third ranked secondary endpoint) between the efficacy of the Low Dose group and the High Dose group show that although remission/response rates were numerically higher in the High Dose group, the differences were not statistically significant.

Table 14: Summary of Subjects in Clinical Remission or Clinical Response at Weeks 4, 26, and 52 by Treatment Group

	Induction Dose at Weeks 0 and 2[a] N = 188			
Week 4				
Clinical Remission[d]	52/188 (27.7)		--	--
Clinical Response[e]	155/188 (82.4)			
	Low Maintenance Dose[c] (20 or 10 mg every other week) N = 95 n/N (%)	**High Maintenance Dose[b] (40 or 20 mg every other week) N = 93 n/N (%)**	**Treatment Difference (95% CI)**	**p-value**
Week 26				
Clinical Remission[d]	27/95 (28.4)	36/93 (38.7)	10.29 (–3.14, 23.71)	0.075
Clinical Response[e]	46/95 (48.4)	55/93 (59.1)	10.72 (–3.45, 24.89)	0.073
Week 52				
Clinical Remission[d]	22/95 (23.2)	31/93 (33.3)	10.18 (–2.62, 22.97)	0.100
Clinical Response[e]	27/95 (28.4)	39/93 (41.9)	13.51 (–0.01, 27.04)	0.038*

a. For subjects weighing ≥ 40 kg, induction dose was 160 mg (at Week 0) and 80 mg (at Week 2). For subjects weighing < 40 kg, induction dose was 80 mg (at Week 0) and 40 mg (at Week 2).
b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
d. Clinical remission defined as PCDAI ≤ 10.
e. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.
* Statistically significant at 0.05 level.
Sponsor's response to IR July 31, 2014

6.1.6 Other Endpoints

The clinically relevant endpoints are discussed above.

6.1.7 Subpopulations

Since the adult adalimumab CD study showed a lower remission rate in subjects who had been exposed to prior anti-TNF agents versus those who had not, Study M06-806 also examined this relationship. When subjects with prior infliximab use were compared

to subjects who were naïve to infliximab, the remission/response rates were numerically higher in the subjects who were naïve to infliximab. It also appeared that the dose-response relationship was greater in subjects who were naïve to infliximab in 26 week Clinical Remission and 52 week Clinical Response (with nominal p values). See Table 15 below.

Table 15: Primary and Ranked Secondary Endpoints by Infliximab Use

	Induction Dose at Weeks 0 and 2[a] N = 188			
Week 4				
Clinical Remission[d]			--	--
Prior infliximab use	18/83 (21.7)			
No prior infliximab use	34/105 (32.4)			
Clinical Response[e]				
Prior infliximab use	64/83 (77.1)			
No prior infliximab use	91/105 (86.7)			
	Low Maintenance Dose[c] (20 or 10 mg every other week) N = 95 n/N (%)	**High Maintenance Dose[b] (40 or 20 mg every other week) N = 93 n/N (%)**	**Treatment Difference (95% CI)**	**p-value**
Week 26				
Clinical Remission[d]				
Prior infliximab use	8/41 (19.5)	7/42 (16.7)	–2.85 (–19.40, 13.71)	0.736
No prior infliximab use	19/54 (35.2)	29/51 (56.9)	21.68 (3.05, 40.31)	0.026*
Clinical Response[e]				
Prior infliximab use	12/41 (29.3)	20/42 (47.6)	18.35 (–2.19, 38.90)	0.086
No prior infliximab use	34/54 (63.0)	35/51 (68.6)	5.66 (–12.45, 23.78)	0.541
Week 52				
Clinical Remission[d]				
Prior infliximab use	7/41 (17.1)	8/42 (19.0)	1.97 (–14.57, 18.52)	0.815
No prior infliximab use	15/54 (27.8)	23/51 (45.1)	17.32 (–0.82, 35.46)	0.065
Clinical Response[e]				
Prior infliximab use	9/41 (22.0)	11/42 (26.2)	4.24 (–14.13, 22.61)	0.652
No prior infliximab use	18/54 (33.3)	28/51 (54.9)	21.57 (3.01, 40.13)	0.026*

a. For subjects ≥ 40 kg, induction dose was 160 mg (at Week 0) and 80 mg (at Week 2). For subjects weighing < 40 kg, the induction dose was 80 mg (at Week 0) and 40 mg (at Week 2).
b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
d. Clinical remission defined as PCDAI ≤ 10.
e. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.

* Statistically significant at 0.05 level.
Sponsor's response to IR July 31, 2014

When the results for the primary endpoint and first three ranked secondary endpoints were analyzed by Baseline Body Weight (< 40 kg or ≥ 40 kg), it appeared that the higher Body Weight sub-group had higher remission/response rates compared to the lower Body Weight sub-group. In addition, the High Dose group had higher remission/response rates as compared to the Lower Dose group; however, the differences were not statistically significant. See Table 16 below.

Table 16: Summary of Subjects in Clinical Remission or Clinical Response at Weeks 4, 26, and 52 by Treatment Group and Baseline Body Weight

	Induction Dose at Weeks 0 and 2[a] N = 188			
Week 4				
Clinical Remission[d]			--	--
< 40 kg at baseline	16/67 (23 9)			
≥ 40 kg at baseline	36/121 (29.8)			
Clinical Response[e]				
< 40 kg at baseline	58/67 (86.6)			
≥ 40 kg at baseline	97/121 (80.2)			
	Low Maintenance Dose[c] (20 or 10 mg every other week) N = 95 n/N (%)	**High Maintenance Dose[b] (40 or 20 mg every other week) N = 93 n/N (%)**	**Treatment Difference (95% CI)**	**p-value**
Week 26				
Clinical Remission[d]				
< 40 kg at baseline	9/35 (25.7)	11/32 (34.4)	8.66 (–13.26, 30.58)	0.206
≥ 40 kg at baseline	18/60 (30.0)	25/61 (41.0)	10.98 (–5.95, 27.92)	0.202
Clinical Response[e]				
< 40 kg at baseline	16/35 (45.7)	16/32 (50.0)	4.29 (–19.64, 28.21)	0.394
≥ 40 kg at baseline	30/60 (50.0)	39/61 (63.9)	13.93 (–3.54, 31.41)	0.115
Week 52				
Clinical Remission[d]				
< 40 kg at baseline	6/35 (17.1)	10/32 (31.3)	14.11 (–6.24, 34.45)	0.066
≥ 40 kg at baseline	16/60 (26.7)	21/61 (34.4)	7.76 (–8.59, 24.11)	0.421
Clinical Response[e]				
< 40 kg at baseline	10/35 (28.6)	13/32 (40.6)	12.05 (–10.61, 34.72)	0.113
≥ 40 kg at baseline	17/60 (28.3)	26/61 (42.6)	14.29 (–2.56, 31.14)	0.123

a. For subjects weighing ≥ 40 kg, induction dose was 160 mg (at Week 0) and 80 mg (at Week 2). For subjects weighing < 40 kg, the induction dose was 80 mg (at Week 0) and 40 mg (at Week 2).

b. The high maintenance dose was 20 mg every other week (for subjects weighing < 40 kg at Week 4) and 40 mg (for subjects weighing ≥ 40 kg at Week 4).
c. The low maintenance dose was 10 mg (for subjects weighing < 40 kg at Week 4) and 20 mg (for subjects weighing ≥ 40 kg at Week 4).
d. Clinical remission defined as PCDAI ≤ 10.
e. Clinical response defined as reduction in PCDAI of at least 15 points from baseline.
Sponsor's response to IR on 31 July 2014

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

According to Clinical Pharmacology, the exposure-response relationship between trough concentrations at Week 26 and clinical remission showed that the High Dose group achieved similar trough concentrations as those of adults. In addition, the High Dose group had greater Week 26 clinical remission rates than the Low Dose group. This was consistent with results observed with dose response for clinical remission at Week 26. There was a trend in dose response showing that High Dose provided numerically higher benefit for other secondary endpoints (clinical remission at Week 52, clinical response at Week 26, and clinical response at Week 52). For complete information, see the Clinical Pharmacology Review dated 21 August 2014.

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 from eow to ew dosing. However, these maintenance results were confounded by the lack of re-randomization at Week 12. But, according to Clinical Pharmacology Review by Nitin Mehrotra PhD, at the individual patient level, certain patients benefited from dose escalation. See Clinical Pharmacology Review dated 21 August 2014 for further details.

6.1.10 Additional Efficacy Issues/Analyses

The Sponsor performed an analysis which compared the results of this (pediatric) pivotal trial (M06-806) with the results of the adult pivotal trial (M02-404). In prior discussions, the Division had informed the Sponsor that this analysis would be considered exploratory. See Table 1 in Appendix E for further details.

7 Review of Safety

7.1 Methods

The safety of adalimumab in pediatric subjects with CD was determined using data from two clinical studies: one double-blind, randomized Phase 3 study (Study M06-806), which is complete, and one open-label extension Phase 3 study (Study M06-807), which was ongoing at the time of this submission.

The Sponsor defined four safety analysis sets as follows:

Any Adalimumab Set (N = 192) – Includes all subjects who received at least one dose of adalimumab in Study M06-806 or Study M06-807

M06-806 Safety Analysis Set (N = 188) – Includes all randomized subjects who received at least one dose of DB adalimumab

Dose Escalation Set (N = 118) – Includes all subjects who dose-escalated from eow to ew dosing in Study M06-806 or Study M06-807 or subjects who were in the Low Dose group at Week 52 in Study M06-806 and rolled over to the high OL eow dose in Study M06-807

No Dose Escalation Set (N = 74) – Includes all subjects who did not have dose-escalation in Study M06-806 or Study M06-807

However, only the safety set(s) that is/are most relevant for each analysis will be discussed in this review (mostly the Any **Adalimumab Set** since each of the Dose Escalation sets contains 2 doses which would confound a comparison between them**)** . Note that the **ITT Population** included 188 subjects and the Any **Adalimumab Set** included 192 subjects.

In addition, this reviewer did an extensive analysis of the SAEs, severe AEs, AEs leading to discontinuation, and infectious AEs in the sub-group of subjects whose BW was < 40 kg. This analysis used the **No Dose Escalation Set.**

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from Study M06-806 and Study M06-807 as above.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were classified by the Sponsor using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 13.0 SOC/PT classifications.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from Studies M06-806 and Study M06-807. 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 AEs, clinical laboratory evaluations (hematology, clinical chemistry), vital signs, EKGs and physical examination parameters. AEs of special interest such as malignancies (including Hepatosplenic T-cell lymphoma), opportunistic infections, demyelinating diseases and auto-immune diseases were monitored closely. Patients who were given at least one dose of the study medication were included in the safety analysis populations.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across both studies, a total of 192 pediatric subjects with CD have been exposed to at least 1 dose of adalimumab as of 31 January 2013, for a cumulative exposure of 404 patient years (PYs) Of these subjects, 115 (60%) had at least 12 months of adalimumab exposure, 82 (43%) had at least 24 months of exposure, 75 (39%) had at least 36 months of exposure, and 40 (21%) had at least 48 months of exposure. The median exposure was 434 days (range of 14 to 1,977 days). See Table 17 below for extent of exposure details.

The demographic characteristics in each of the safety analysis sets were the same as those listed in Section 6.1.2.

Table 17: Extent of Exposure (Any Adalimumab Set)

Exposure to Study Drug	Any Adalimumab Set N = 192
Duration of treatment (days)	
Mean ± SD	767.7 ± 633.33
Median (min – max)	434.0 (14 – 1977)
Total number of injections	
Mean ± SD	71.2 ± 60.40
Median (min – max)	46.5 (1 – 257)
Average monthly dose (mg)	
Mean ± SD	90.65 ± 38.717
Median (min – max)	82.95 (1.0 – 320.0)
Duration of Exposure	n (%)
≥ 1 day	192 (100)
> 15 days	189 (98.4)
> 29 days	188 (97.9)
> 57 days	174 (90.6)
> 85 days	165 (85.9)
> 113 days	163 (84.9)
> 141 days	156 (81.3)
> 169 days	149 (77.6)
> 197 days	146 (76.0)
> 225 days	141 (73.4)
> 253 days	136 (70.8)
> 281 days	132 (68.8)
> 309 days	126 (65.6)
> 337 days	124 (64.6)
> 365 days (at least 12 months)	115 (59.9)
> 456 days	95 (49.5)
> 547 days (at least 18 months)	91 (47.4)
> 638 days	83 (43.2)
> 729 days (at least 24 months)	82 (42.7)
> 820 days	78 (40.6)

Duration of Exposure	Any Adalimumab Set N = 192 n (%)
> 911 days	78 (40.6)
> 1002 days	77 (40.1)
> 1093 days (at least 36 months)	75 (39.1)
> 1184 days	68 (35.4)
> 1275 days	65 (33.9)
> 1366 days	63 (32.8)
> 1457 days (at least 48 months)	40 (20.8)
> 1548 days	30 (15.6)
> 1639 days	21 (10.9)
> 1730 days	10 (5.2)
> 1821 days (at least 60 months)	8 (4.2)
Total number of patient years	403.5

Max = maximum; min = minimum; SD = standard deviation

Notes: Includes Study M06-806 and Study M06-807.

Exposure is defined as the date of the last adalimumab dose minus the date of the first adalimumab dose in Study M06-806 + 14 days. If the last adalimumab dose date occurred in Study M06-807, a between-studies dosing gap > 14 days is excluded. The adalimumab dose dates after 31 January, 2013 were not used to calculate exposure if a subject is still ongoing in Study M06-807 as of that cutoff date.

Average monthly dose = total dose × 28 days ÷ duration.

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Extent of exposure by treatment group is displayed in Table 18 below.

Table 18: Extent of Exposure (Safety Analysis Set)

Induction Period,[a] N = 192							
Exposure to Study Drug				**Mean ± SD**			
Duration (days)				27.8 ± 2.16			
Total number of injections				4.9 ± 1.48			
Total dose adalimumab (mg)				195.7 ± 59.66			
Maintenance Period,[b] N = 188							
	Low-Dose Adalimumab 10 mg or 20 mg eow			**High-Dose Adalimumab 20 mg or 40 mg eow**			**All Adalimumab**
	10 mg N = 31	**20 mg N = 64**	**Total N = 95**	**20 mg N = 29**	**40 mg N = 64**	**Total N = 93**	**N = 188**
Exposure to Study Drug				**Mean ± SD**			
Duration (days)	166.5 ± 123.08	190.4 ± 124.92	182.6 ± 124.17	184.8 ± 136.56	225.2 ± 122.19	212.6 ± 127.49	197.4 ± 126.39
Total number of adalimumab injections	11.8 ± 8.81	13.5 ± 8.90	13.0 ± 8.86	13.1 ± 9.75	15.8 ± 8.78	15.0 ± 9.13	14.0 ± 9.03
Total dose adalimumab (mg)	126.8 ± 104.54	270.6 ± 177.91	223.7 ± 171.16	271.7 ± 210.48	632.5 ± 351.31	520.0 ± 355.30	370.3 ± 314.49

SCS Table 6 pg 30

7.2.2 Explorations for Dose Response

There was only one induction dosing regimen per weight sub-group (<40 kg or ≥ 40 kg). However, for maintenance, within each weight sub-group, there was a High Dose group and a Low Dose group. There appeared to be a dose response relationship wherein the High Dose group had a numerically higher remission/response rate than the Low Dose group. However, the difference between dose groups was not statistically significant.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this sBLA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments. See Section 5.3.1 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see the Clinical Pharmacology Review

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 potential adverse effects known to be related to anti-TNF antibody agents such as: opportunistic infections, injection site reactions, systemic lupus erythematosus, allergic reactions, hematologic-related adverse events, elevated ALT levels, worsening of psoriatic conditions, and pancreatitis. No new potential AEs for TNF-antagonists were identified from this pediatric trial (and extension trial).

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in Study M06-806 or Study M06-807.

7.3.2 Nonfatal Serious Adverse Events

In the Any Adalimumab Set, CD flare was reported as an SAE in 57 subjects (30%). Anemia, abdominal abscess, abdominal pain, anal abscess, tachycardia, gastritis, pneumonia, and small intestinal obstruction were each reported in more than 1 subject (2-4 subjects); all other SAEs were reported in only 1 subject each. Whether some of these SAEs (anemia, abdominal abscess, abdominal pain, anal abscess, gastritis, and small intestinal obstruction) were actually treatment related is difficult to discern because the events could have been secondary to the subject's underlying disease process. See Table 1 in Appendix F for further details.

When this reviewer compared rates of TEAEs (in subjects who did not Dose Escalate) between the High Dose group and the Low Dose group in each of the Baseline Weight groups (≥ 40 kg or < 40kg), it initially appeared that there was an imbalance between treatment groups in SAEs, Severe AEs, AEs leading to discontinuation and Infectious AEs in the< 40kg Baseline Weight group. See Table 1 in Appendix G. Therefore this reviewer further investigated each event individually**. After this further evaluation, it appeared that many of the AEs in the High Dose group were secondary to worsening of CD or URI/nasopharyngitis. In addition, the number of subjects in each treatment group was small (N=12; N=19) and the numbers were not balanced, so that it would be difficult to draw accurate conclusions from this data. Thus, the apparent differences in AEs rates may not be significant**. See Table 19 below for further details.

Table 19: Adverse Events in Subjects with Baseline Weight < 40 kg and No Dose-Escalation

AE Category	Low Dose (10 mg) N=12	High Dose (20 mg) N=19
Severe AE	3 patients with worsening CD	4 patients with worsening CD upper abdominal pain, asthenia, decreased appetite, diarrhea and vomiting H1N1 flu multiple infections in one subject, all resolved anal abscess
SAEs	same 2 patients above with worsening CD	5 patients with worsening CD (3 from above severe AEs) H1N1 flu psychosomatic dx

AE leading to discontinuation of study drug	same 2 patients above with worsening CD	5 patients with worsening CD from above upper abdominal pain, asthenia, decreased appetite, diarrhea and vomiting H1N1 flu
Infectious AE	allergies and URI viruses, (URI, Otitis media) 2 URI viruses tinea	allergies and URI 3 worsening CD, from above H1N1 flu multiple infections in one subject, all resolved, anal abscess, 2 nasopharyngitis 2 URI pharyngitis

Table compiled by this Reviewer from Sponsor's Response to IR dated 3 April 2014

7.3.3 Dropouts and/or Discontinuations

In the Any Adalimumab Set, 55 subjects (29%) had AEs leading to discontinuation. CD flare led to the discontinuation of 38 subjects (20%); all other events led to discontinuation of 1 or 2 subjects.

Of the 33 subjects (17%) who had SAEs leading to discontinuation in the Any Adalimumab Set, 27 subjects had a CD flare. Other SAEs leading to discontinuation included abdominal abscess in 2 subjects and small intestinal obstruction, H1N1 influenza, histoplasmosis disseminated, and systemic lupus erythematosus in 1 subject each.

7.3.4 Significant Adverse Events

Significant Adverse Events of special interest for adalimumab are included below. These events include those described in the current labeling in WARNINGS AND PRECAUTIONS as well as other events which had been specifically monitored for this application.

No treatment-emergent malignancies, HSTCL, leukemia, melanoma, cutaneous vasculitis, diverticulitis, intestinal perforation, MI, CVA, pulmonary embolism, demyelinating disease, Stevens-Johnson syndrome, erythema multiforme, CHF, or interstitial lung disease AEs were reported.

Serious Infections

In the Any Adalimumab Set, abdominal abscess and anal abscess were each reported as serious infections in 3 subjects (2%), and pneumonia was reported as a serious infection in 2 subjects (1%). Whether abdominal abscess and anal abscess were actually treatment related is difficult to discern because the events could have been secondary to the subject's underlying disease process All other serious infections were reported in only 1 subject each. See Table 20 below.

Table 20: Subjects with Treatment-Emergent Serious Infections (Any Adalimumab Set)

Preferred Term	Any Adalimumab Set N = 192 n (%)
Any serious infection	21 (10.9)
Abdominal abscess	3 (1.6)
Anal abscess	3 (1.6)
Pneumonia	2 (1.0)
Bartholin's abscess	1 (0.5)
Cystitis viral	1 (0.5)
Device related sepsis	1 (0.5)
Gastroenteritis	1 (0.5)
H1N1 influenza	1 (0.5)
Herpes virus infection	1 (0.5)
Histoplasmosis disseminated	1 (0.5)
Impetigo	1 (0.5)
Salmonellosis	1 (0.5)
Scarlet fever	1 (0.5)
Sinusitis	1 (0.5)
Staphylococcal abscess	1 (0.5)
Subcutaneous abscess	1 (0.5)
Tonsillitis	1 (0.5)
Tooth abscess	1 (0.5)
Viral infection	1 (0.5)
Yersinia infection	1 (0.5)

Notes: Includes Study M06-806 and Study M06-807.
TEAE is defined as any AE with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date on or before 31 January 2013 was used if a subject was still ongoing in Study M06-807. Adverse events with an onset date more than 70 days during the gap between studies were excluded.

SCS Table 34 pg 103

Although the investigators may have determined that the occurrence of a particular AE was potentially related to treatment with adalimumab, causality is difficult to determine with infections which are commonplace in the general population and in a Crohn's disease population.

Opportunistic Infections

In the Any Adalimumab Set, 8 subjects reported opportunistic infection related AEs: a 16-year-old white female developed an SAE of histoplasmosis disseminated, a 12-year-old white female developed an Aeromona infection, four subjects had oral candidiasis (including 1 subject with multiple episodes), one subject had esophageal candidiasis and 1 subject had fungal esophagitis.

Injection Site Reaction-Related Events
In the Any Adalimumab Set, the most frequently reported injection site reaction related TEAEs were injection site reaction, reported in 22 subjects (12%), and injection site pain, reported in 15 subjects (8%).

Lupus-Like Syndrome
In the Any Adalimumab Set, a 14-year-old white female, experienced a serious TEAE of systemic lupus erythematosus during Study M06-807 (Day 534 of adalimumab treatment) The subject experienced worsening of pre-existing arthritis on Day 522 and increased CRP on Day 534. The subject's ANA titer was negative (< 1:40) on Day 1 and was > 1:2560 on Day 534.The last dose of study drug was administered on Day 534. The subject discontinued study drug due to the event. The event was ongoing as of Day 667.

Allergic Reaction Related
In the Any Adalimumab Set, 40 subjects (21%) experienced allergic reaction related TEAEs: rash, hypersensitivity, urticaria, and erythema were the most frequently reported allergic reaction related TEAEs, occurring in 7%, 4%, 4%, and 3% of subjects, respectively.

Hematologic-Related Events
In the Any Adalimumab Set, 30 subjects (16%) experienced a hematologic related TEAEs. Seventeen subjects (9%) had anemia, and nine subjects (5%) had leukopenia. Four subjects who all had a history of anemia experienced SAEs of anemia, which resolved within a few days.

Intestinal Strictures
In the Any Adalimumab Set, four subjects (2%) experienced intestinal stricture related TEAEs; two reported small intestinal obstructions, one subject experienced small intestinal stenosis and one subject had colonic stenosis.

Hepatic-Related Events
In the Any Adalimumab Set, one subject with a medical history of hepatitis and concurrently receiving long-term methotrexate therapy had a serious hepatic related event. The subject developed elevated transaminases, was hospitalized, and infectious causes were ruled out. Study drug was interrupted and reintroduced after resolution of the event. Of note, the event took place during dose escalation.

Elevated ALT

In the Any Adalimumab Set, nine subjects (5%) experienced elevated ALT related TEAEs. None of the events were serious, and no subjects discontinued due to these events. Two subjects had prior exposure to infliximab and one subject had a history of liver disease. All subjects took concomitant medication of hepatotoxic potential (seven subjects took concomitant IMM (AZA, 6-MP, MTX) or had just stopped IMM several days before the lab assessment, and two subjects took paracetamol on a regular basis).

Pancreatitis
A 14-year-old Asian male with a history of repeat episodes of pancreatitis and with prior infliximab exposure, experienced an event of pancreatitis acute on Day 221 of DB treatment with 20 mg adalimumab (Low Dose. The event ended on Day 225. The subject did not discontinue study drug due to this event.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

TEAEs reported by ≥ 5% of subjects in the Any Adalimumab Set are presented in Table 21 below. Crohn's disease was the most frequently reported TEAE, occurring in 52% of subjects. This PT represented a flare or worsening of the underlying disease.

Table 21: Treatment-Emergent Adverse Events Reported by ≥ 5% of Subjects, by Descending Order of Frequency (Any Adalimumab Set)

MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Crohn's disease	100 (52.1)
Headache	51 (26.6)
Upper respiratory tract infection	41 (21.4)
Nasopharyngitis	39 (20.3)
Diarrhoea	33 (17.2)
Nausea	32 (16.7)
Oropharyngeal pain	32 (16.7)
Pyrexia	32 (16.7)
Abdominal pain	29 (15.1)
Vomiting	29 (15.1)
Cough	28 (14.6)
Arthralgia	25 (13.0)
Fatigue	22 (11.5)
Injection site reaction	22 (11.5)
Abdominal pain upper	21 (10.9)
Constipation	21 (10.9)
Viral infection	21 (10.9)
Sinusitis	19 (9.9)
Pharyngitis	18 (9.4)
Anemia	17 (8.9)
Back pain	17 (8.9)
Pharyngitis streptococcal	16 (8.3)
Rash	16 (8.3)
Injection site pain	15 (7.8)
Urinary tract infection	15 (7.8)
Viral upper respiratory tract infection	15 (7.8)
Influenza	14 (7.3)
Nasal congestion	14 (7.3)

MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Pain in extremity	14 (7.3)
C-reactive protein increased	13 (6.8)
Eczema	13 (6.8)
Lymphadenopathy	13 (6.8)
Rhinorrhea	13 (6.8)
Skin papilloma	13 (6.8)
Dizziness	12 (6.3)
Otitis media	12 (6.3)
Bronchitis	11 (5.7)
Conjunctivitis	11 (5.7)
Procedural pain	11 (5.7)
Rhinitis	11 (5.7)
Anal fissure	10 (5.2)
Decreased appetite	10 (5.2)
Gastroenteritis	10 (5.2)
Muscle spasms	10 (5.2)

Notes: Includes Study M06-806 and Study M06-807.
TEAE is defined as any AE with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date on or before 31 January 2013 was used if a subject was still ongoing in Study M06-807. Adverse events with an onset date more than 70 days during the gap between studies were excluded.

CSR Table 27 pg 80-81

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinically significant abnormalities, and changes over time were reviewed for clinical chemistry and hematology. The individual cases of anemia were reviewed and most cases either resolved or occurred in patients with a prior history of anemia. In addition, the individual cases of potentially clinically significant elevations in liver function tests were reviewed. With the exception of one subject who took concomitant IMM and whose ALT value remained > 5 × ULN through the last post-treatment assessment, all potentially clinically significant liver values had returned to normal by the end of treatment. Consequently, there were no clinically important findings that have not been described in current labeling.

7.4.3 Vital Signs

Vital sign trends were reviewed. Although certain subjects had decreases in diastolic BP reported, these were isolated values in each patient and thus were not clinically relevant. No clinically important findings were seen.

7.4.4 Electrocardiograms (ECGs)

Adalimumab is an approved product with no known effects on ECG findings. ECG data was recorded at screening and not repeated

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

According to Clinical Pharmacology Review dated 21 August 2014:
"In Study M06-806, 182 subjects had the immunogenicity samples collected according planned schedule in the protocol. Of these 182 subjects, 58 subjects had at least one sample tested for ADA. A total of 6 subjects among the 58 subjects with samples tested were determined as ADA positive; therefore, the incidence of ADA development was 10% (6/58). The applicant also provided an alternate calculation of ADA formation rate based on the 182 subjects who received adalimumab treatment, which reported the ADA development rate of 3% (6/182). The remaining 124 subjects were not tested for ADA because all their immunogenicity samples had adalimumab concentration ≥ 2 mcg/mL which prevents the detection of ADA. Due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL.

The PK results indicated that ADA formation was associated with decreased adalimumab exposure in pediatric subjects with CD. The majority of PK samples in ADA positive subjects had serum adalimumab concentrations declined to below the lower limit of quantitation (LLOQ, 31.25 ng/mL) of the PK assay. The number of subjects who had ADA samples tested and confirmed to have developed ADA was too small to determine the effect of ADA on the efficacy or safety of adalimumab in pediatric subjects with CD. The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application."

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no clear trend of higher incidence of AEs with increasing adalimumab dose. However, due to the study design which included two different doses in both the Low and High Dose treatment arms and an option for dose escalation, clear trends would be difficult to discern.

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 Sponsor 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 adalimumab 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. Adalimumab 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

Improvement (increase) in z-score for height velocity was observed for both treatment groups at Week 26. No difference was observed between treatment groups in mean change at Week 26 from Baseline in z-score for height velocity.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the Sponsor, as of the 31 January 2013 data cut-off, there were no reports of overdose in the CD pediatric studies, and the relevant information in the prescribing information remains unaltered. There is no evidence for, and no anticipation of, subject abuse of adalimumab. No withdrawal effects are anticipated with the use of adalimumab other than the potential for deterioration in control of CD symptoms following the discontinuation of the drug if appropriate follow-up is not instituted.

8 Postmarket Experience

Adalimumab was first approved for treatment of rheumatoid arthritis (RA) in the United States on 31 December 2002 (international birth date). Through 31 December 2012 (cut-off date for most recent postmarketing safety update report), adalimumab has been approved in 90 countries. In addition to the postmarketing experience gained in the pediatric CD population since the initial European Union approval of this indication in 2012, extensive postmarketing experience has been amassed in the much larger CD and RA populations as well as patients with other approved indications, amounting to a cumulative exposure of (b) (4) between 31 December 2002 and 31 December 2012. The safety profile for adalimumab is similar across indications; therefore, the safety data in RA patients and other approved indications such as psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and juvenile idiopathic arthritis are considered supportive for the pediatric CD indication.

9 Appendices

9.1 Literature Review/References

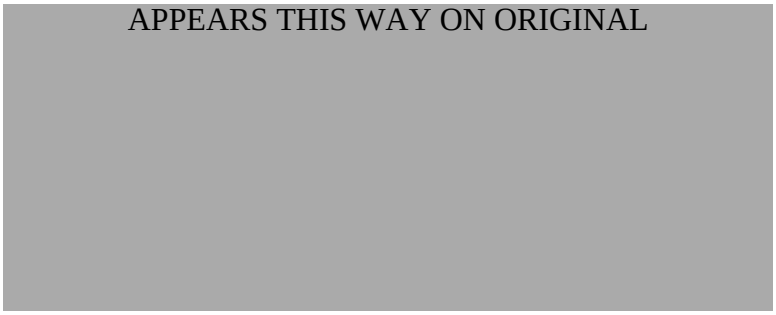
See individual references noted throughout this review.

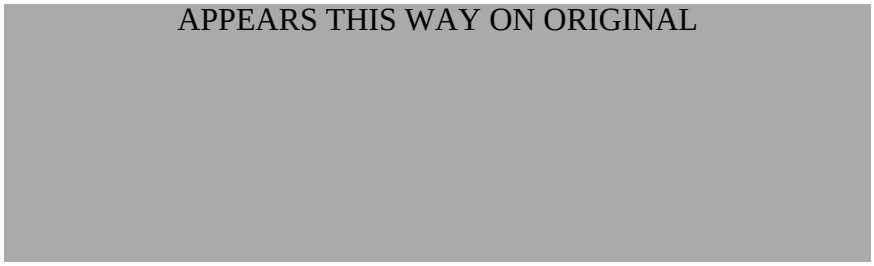
9.2 Labeling Recommendations

At the time of this review labeling was not yet negotiated with the Sponsor.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

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Appendix A

Exclusion Criteria Continued

Received previous treatment with adalimumab or previous participation in an adalimumab clinical study.

Screening laboratory and other analyses showing any of the following abnormal results:

- ECG – with clinically significant abnormalities
- Aspartate transaminase (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range
- Total bilirubin ≥ 3 mg/dL
- Serum creatinine > 1.6 mg/dL

Subjects on AZA, 6-MP, or MTX who had not been on these medications for at least 88 weeks prior to Baseline and on stable doses of these medications for at least 44 weeks prior to Baseline. Subjects who had been on AZA, 6-MP, or MTX and who had discontinued these medications within 8 weeks of Baseline.

Subjects on aminosalicylates, or CD-related antibiotics (fluoroquinolones such as ciprofloxacin or nitroimidazole derivatives such as metronidazole) that had not been on stable doses of these medications for at least 4 weeks prior to Baseline. In addition, subjects on aminosalicylates or CD-related antibiotic treatments that had discontinued these medications within 4 weeks of Baseline.

Subjects on prednisone > 40 mg/day (or equivalent) or subjects on < 10 mg/day prednisone and subjects who were not on a stable dose for at least 2 weeks prior to Baseline. In addition, subjects who discontinued prednisone (or equivalent) within 2 weeks of Baseline.

Subjects on growth hormone that had not been on a stable dose for at least 12 weeks prior to Baseline. Subjects had to consent to remain on a stable dose through the duration of the study.

Subjects on budesonide > 9 mg/day and subjects who were not on stable doses for at least 2 weeks prior to Baseline. In addition, subjects who discontinued budesonide within 2 weeks of Baseline.

Subjects who were currently taking both budesonide and prednisone (or equivalent).

Subjects who had undergone therapeutic enemas within 2 weeks prior to Baseline.

Subjects who had been on cyclosporine (intravenous [IV], oral), tacrolimus (any form), or mycophenolate mofetil within 28 days of Baseline.

Subjects who had been on Kineret® (anakinra) must discontinue use 2 days prior to Baseline.

Subjects with any prior exposure to Tysabri (natalizumab).

Subjects with known hypersensitivity to the excipients of adalimumab as stated in the label.

Subjects with a previous history of dysplasia of the GI tract.

Subjects who weighed < 17 kg at Screening.

Appendix B

Ranked Secondary Efficacy Variables

The ranked secondary endpoints No. 1 to No. 3 and No. 6 to No. 8 were comparisons between the High-Dose and Low-Dose treatment groups, and ranked secondary endpoints No. 4 and No. 5 were comparisons to the adult Study M02-404 ("external analyses").

1. Proportion of subjects in PCDAI clinical remission at Week 52
2. Proportion of subjects in PCDAI clinical response at Week 26
3. Proportion of subjects in PCDAI clinical response at Week 52
4. Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders
5. PCDAI clinical remission at Week 4
6. Proportion of subjects receiving corticosteroids at Baseline who have discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and are in PCDAI clinical remission at Week 26
7. Change from Baseline in z-scores for height velocity at Week 26
8. Change from Baseline in total IMPACT III scores at Week 26

Additional Secondary Endpoints

- Proportion of subjects in PCDAI clinical remission at Week 26 who are also in PCDAI clinical remission at Week 52 (and never had a flare between Week 26 and Week 52).
- Time in PCDAI clinical remission while on DB eow treatment.
- Time to PCDAI clinical remission while on DB eow treatment.
- Time to steroid-free PCDAI clinical remission while on DB eow treatment.
- Proportion of subjects in PCDAI clinical response over time.
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids and were in PCDAI clinical remission at Weeks 12, 26, and 52.
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids and were in PCDAI clinical remission at Week 26 and who remained off corticosteroids and were in PCDAI clinical remission at Week 52.
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 52 and were in PCDAI clinical remission at Week 52.
- Change from Baseline in serological markers of bone metabolism (osteocalcin, BSAP, and NTx) at Week 26 and Week 52.

- Change from Baseline in total IMPACT III scores at Week 12 and Week 52.
- Change from Baseline in WPAI Questionnaire scores (absenteeism, presenteeism, total work impairment, and activity impairment) over time.
- Cumulative number of unscheduled outpatient visits (physician visits, emergency room visits, hospital admissions, and days of hospitalization) up to Week 52.
- Change from Baseline in BMI at Week 26 and Week 52.
- Change from Screening in bone age at Week 52.
- Change from Baseline in z–score for height velocity 52.
- Change from Baseline in corticosteroid dose at Week 26 and Week 52 (only for subjects who have not discontinued corticosteroids at these time points).
- Proportion of subjects with fistula remission (defined as the closure of all fistulas that were draining at Baseline for at least 2 consecutive visits) while receiving DB eow treatment.
- Proportion of subjects with improvements in the number of draining fistulas (defined as a decrease from Baseline in the number of draining fistulas of ≥ 50% for at least 2 consecutive visits) while receiving DB eow treatment.
- Proportion of subjects who dose escalated in the DB period from eow to ew. (Note: dose readjustment at Week 26 based on the Week 26 BW is not considered a dose-escalation.)
- Proportion of subjects in PCDAI clinical remission at Week 52 after dose escalation for:
    - Subjects who had not achieved PCDAI clinical response prior to dose escalation
    - Subjects who achieved PCDAI clinical response, but lost response prior to dose escalation
- Proportion of subjects who switched to OL dosing and were in PCDAI clinical remission at Week 52 for:
    - Subjects who had not achieved PCDAI clinical response prior to OL dosing and
    - Subjects who achieved PCDAI clinical response but lost response prior to OL dosing
- Proportion of subjects receiving IMM at Baseline who had discontinued IMM and were in PCDAI clinical remission at Week 52.
- Change from Baseline in CRP levels at Weeks 4, 26, and 52.

Appendix C

Table 6. History of Infliximab Use (Study M06-806: ITT Analysis Set)

	Number (%) of Subjects			
	Low Dose Adalimumab 20 mg or 10 mg eow N = 95	High Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188	*P* value[a]
Prior infliximab use				0.883
Yes	41 (43.2)	42 (45.2)	83 (44.1)	
No	54 (56.8)	51 (54.8)	105 (55.9)	
Initial response to infliximab				0.494
Yes	40 (97.6)	42 (100.0)	82 (98.8)	
No	1 (2.4)	0	1 (1.2)	
Loss of response to infliximab				1.000
Yes	33 (80.5)	34 (81.0)	67 (80.7)	
No	8 (19.5)	8 (19.0)	16 (19.3)	
Reaction to infliximab				0.817
Yes	13 (31.7)	15 (35.7)	28 (33.7)	
Acute	6 (46.2)	12 (80.0)	18 (64.3)	
Delayed	7 (53.8)	3 (20.0)	10 (35.7)	
No	28 (68.3)	27 (64.3)	55 (66.3)	
Loss of response and reaction				1.000
Yes	7 (17.1)	7 (16.7)	14 (16.9)	
No	34 (82.9)	35 (83.3)	69 (83.1)	

a. The *P* value is based on Fisher's exact test.

Note: Percentages calculated based on non-missing values.

Table 7. Concomitant Immunosuppressant and Systemic Corticosteroid Use at Baseline (Study M06-806: ITT Analysis Set)

	Number (%) of Subjects		
Subjects Entering Study	Low Dose Adalimumab 20 mg or 10 mg eow N = 95	High Dose Adalimumab 40 mg or 20 mg eow N = 93	All Adalimumab N = 188
With IMM	57 (60.0)	60 (64.5)	117 (62.2)
With systemic corticosteroid	38 (40.0)	33 (35.5)	71 (37.8)
Without IMM and without systemic corticosteroid	20 (21.1)	15 (16.1)	35 (18.6)
Without IMM and with systemic corticosteroid	18 (18.9)	18 (19.4)	36 (19.1)
With IMM and without systemic corticosteroid	37 (38.9)	45 (48.4)	82 (43.6)
With IMM and with systemic corticosteroid	20 (21.1)	15 (16.1)	35 (18.6)

Appendix D

Loss of Response

1. A response to a dose of ≥ 5 mg/kg infliximab in the judgment of the investigator

AND

2. A demonstrated loss of this response documented as described below:

- A subject must have received at least 2 subsequent and sequential doses of ≥ 5 mg/kg infliximab at an interval not to exceed every 8 weeks (56 days ± 6 days)

AND

- Experienced a lack of improvement or worsening, in the opinion of the investigator, in one of the following, but not all-inclusive, CD-related signs/symptoms ≥ 2 weeks after the last dose of infliximab: stool frequency, abdominal pain, fever, drainage from a previously non-draining fistula or development of a new draining fistula, rectal bleeding, or increased use or new introduction of anti-diarrheal medication.

Intolerance to Infliximab

A patient was defined as intolerant to infliximab when, in the opinion of the investigator, infliximab therapy had been discontinued by a physician as a result of a significant adverse reaction to infliximab administration. A reaction was considered significant if at least one of the clinical characteristics listed below was reported by history as documented in patient progress notes or other source documents.

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Appendix E

Table 1: External Comparison of the Proportion of Subjects in PCDAI Clinical Remission at Week 26 - NRI (ITT Analysis Set)

Adalimumab	N	Proportion of Subjects in Remission[a]	Difference[b]	95% CI[c]
Study M02-404 (40 mg eow [ITT])	260	33.46	--	--
Study M06-806 Low-Dose	95	44.66	11.20	-0.33, 22.73
Study M06-806 High-Dose	93	46.77	13.31	1.66, 24.96
Study M06-806 Overall	188	46.17	12.71	3.56, 21.86

CI = confidence interval; eow = every other week; ITT = intent-to-treat; NRI = non-responder imputation; PCDAI = Pediatric Crohn's Disease Activity Index

a. For Study M02-404, the proportion of subjects in remission is based on CDAI clinical remission on ITT analysis and for Study M06-806, the proportion of subjects in remission is based on the adjusted PCDAI clinical remission.

b. Difference is between Study M06-806 adalimumab dose group and Study M02-404 (40 mg eow [ITT]).

c. The CI is based on normal approximation.

CSR Table 25 pg 236

Appendix F

Table 1: Summary of Subjects with Treatment-Emergent Serious Adverse Events (Any Adalimumab Set)

System Organ Class MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Any SAE	86 (44.8)
Blood and Lymphatic System Disorders	
Anemia	4 (2.1)
Iron deficiency anemia	1 (0.5)
Lymphadenitis	1 (0.5)
Cardiac Disorders	
Tachycardia	2 (1.0)
Ear and Labyrinth Disorders	
Vertigo	1 (0.5)
Gastrointestinal Disorders	
Crohn's disease	57 (29.7)
Abdominal pain	2 (1.0)
Gastritis	2 (1.0)
Small intestinal obstruction	2 (1.0)
Abdominal pain upper	1 (0.5)
Colitis ulcerative	1 (0.5)
Colonic stenosis	1 (0.5)
Esophagitis	1 (0.5)
Inflammatory bowel disease	1 (0.5)
Pancreatitis acute	1 (0.5)
Peritonitis	1 (0.5)
Rectal haemorrhage	1 (0.5)
Small intestinal stenosis	1 (0.5)
Stomatitis	1 (0.5)

Table 1(Cont'd): Summary of Subjects with Treatment-Emergent Serious Adverse Events (Any Adalimumab Set)

System Organ Class MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
General Disorders and Administration Site Conditions	
Fatigue	1 (0.5)
Pyrexia	1 (0.5)
Hepatobiliary Disorders	
Hepatitis	1 (0.5)
Infections and Infestations	
Abdominal abscess	3 (1.6)
Anal abscess	3 (1.6)
Pneumonia	2 (1.0)
Bartholin's abscess	1 (0.5)
Cystitis viral	1 (0.5)
Device related sepsis	1 (0.5)
Gastroenteritis	1 (0.5)
H1N1 influenza	1 (0.5)
Herpes virus infection	1 (0.5)
Histoplasmosis disseminated	1 (0.5)
Impetigo	1 (0.5)
Salmonellosis	1 (0.5)
Scarlet fever	1 (0.5)
Sinusitis	1 (0.5)
Staphylococcal abscess	1 (0.5)
Subcutaneous abscess	1 (0.5)
Tonsillitis	1 (0.5)
Tooth abscess	1 (0.5)
Viral infection	1 (0.5)
Yersinia infection	1 (0.5)

Table 1 (Cont'd): Summary of Subjects with Treatment-Emergent Serious Adverse Events (Any Adalimumab Set)

System Organ Class MedDRA Preferred Term	Any Adalimumab Set N = 192 n (%)
Injury, Poisoning and Procedural Complications	
Concussion	1 (0.5)
Contusion	1 (0.5)
Facial bones fracture	1 (0.5)
Upper limb fracture	1 (0.5)
Investigations	
Heart rate irregular	1 (0.5)
Musculoskeletal and Connective Tissue Disorders	
Osteoarthritis	1 (0.5)
Systemic lupus erythematosus	1 (0.5)
Nervous System Disorders	
Dizziness	1 (0.5)
Syncope	1 (0.5)
Psychiatric Disorders	
Psychosomatic disease	1 (0.5)
Psychotic disorder	1 (0.5)
Suicidal ideation	1 (0.5)

SAE = serious adverse event

Notes: Includes Study M06-806 and Study M06-807.

TEAE is defined as any AE with an onset date on or after the first adalimumab dose and up to 70 days after the last dose of adalimumab. The last available dose date on or before 31 January 2013 was used if a subject was still ongoing in Study M06-807. Adverse events with an onset date more than 70 days during the gap between studies were excluded.

SCS Table 30 pg 89-91

Appendix G

Table 1: Proportion of Subjects with TEAEs by Baseline Weight < 40 kg and Dose Maintenance Period in Study M06-806 (Safety Analysis Set)

	n/N (%)							
	Baseline Weight < 40 kg[a]							
	No Dose-Escalation				Dose-Escalation			
AE Category	ADA Low 10 mg N = 12	ADA High 20 mg N = 19	ADA Low 20 mg N = 2	ADA High 40 mg N = 2	ADA Low 10 mg N = 19	ADA High 20 mg N = 10	ADA Low 20 mg N = 2	ADA High 40 mg N = 1
Any adverse event	10 (83.3)	17 (89.5)	2 (100)	2 (100)	14 (73.7)	9 (90.0)	2 (100)	0
At least possibly drug-related[b]	5 (41.7)	6 (31.6)	0	1 (50.0)	6 (31.6)	3 (30.0)	0	0
Severe adverse event	3 (25.0)	8 (42.1)	0	0	1 (5.3)	1 (10.0)	0	0
Serious adverse event	2 (16.7)	7 (36.8)	0	0	2 (10.5)	3 (30.0)	1 (50.0)	0
Leading to discontinuation of study drug	2 (16.7)	7 (36.8)	0	0	1 (5.3)	1 (10.0)	1 (50.0)	0
At least possibly drug-related SAE[b]	0	0	0	0	0	0	0	0
Infectious adverse event	6 (50.0)	13 (68.4)	2 (100)	2 (100)	8 (42.1)	6 (60.0)	0	0
Serious infections	0	2 (10.5)	0	0	1 (5.3)	0	0	0
Malignancies	0	0	0	0	0	0	0	0
Lymphomas	0	0	0	0	0	0	0	0
NMSC	0	0	0	0	0	0	0	0
Malignancies (excluding NMSC and lymphomas)	0	0	0	0	0	0	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0	0	0	0	0	0	0
Injection site reactions	1 (8.3)	1 (5.3)	0	0	1 (5.3)	0	0	0
Opportunistic infections, excluding TB	0	0	0	0	0	0	0	0
Congestive heart failure	0	0	0	0	0	0	0	0

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/s/

MARJORIE F DANNIS
08/29/2014

ANIL K RAJPAL
08/29/2014
I concur with Dr. Dannis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

PRODUCT QUALITY 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: May 29, 2014
To: File for STN: sBLA 125057/356
RPM: Matthew Brancazio, Pharm D., CDER/ODEIII/DGIEP
From: Jun Park, Ph.D., Product Reviewer, CDER/OBP/DMA
Through: Laurie, Graham, Team Leader, CDER/OBP/DMA
Sarah Kennett, Ph.D., Chief, CDER/OBP/DMA
Applicant: AbbVie, Inc.
Product: Humira® (adalimumab)
Supplement Receipt Date: August 29, 2013
Action Due Date: June 29, 2014
RECOMMENDATION: This sBLA submission is recommended for approval from a CMC perspective

SUMMARY:

The purpose of this sBLA is to submit an efficacy supplement for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4) (b) (4).

Humira is currently licensed at 50 mg/mL as either

- 40 mg/0.8 mL prefilled syringe
- 20 mg/0.4 mL prefilled syringe
- 20 mg/0.4 mL prefilled pen
- 40 mg/0.8 mL glass vial (institutional use only)

Clinical studies to support the new indication included Study M06-806 and associated extension study (M06-807). Specifically

- Study M06-806 included 2 induction doses at baseline and week 2. The induction doses were based on body weight with subjects weighing ≥ 40 kg receiving induction doses of 160 mg and 80 mg while subjects weighing < 40 kg received 80 mg and 40 mg. Induction dosing was performed with DP in vials at 50 mg/mL.
- Study M06-806 included maintenance doses every other week based on body weight. Subjects ≥ 40 kg could receive either 40 mg or 20 mg, subjects weighing < 40 kg, could

receive either 20 mg or 10 mg. Maintenance dosing also used vials but included the use of both 50 mg/mL and 25 mg/mL vials.

- Study M07-807 included 10, 20, or 40 mg doses every other week. In this case, the 20 and 40 mg doses were given with DP in PFS at 50 mg/mL while the 10 mg dose was given with vial material at 50 mg/mL.

To support the dosing of this indication, a newly developed 10 mg PFS is introduced in this supplement. The formulation and container closure of the drug product in the proposed **10 mg/0.2mL PFS presentation** is identical to the approved Humira presentations. A description of the manufacturing process for the 10 mg/0.2 mL PFS in the submission included testing results for the characterization/comparability, process validation, batch release, and stability. It should be noted that there does not appear to be any clinical experience with the 10 mg PFS. The sponsor is relying upon clinical data for a 10 mg maintenance dose that is based on either the 50 mg/mL vial or a 25 mg/mL vial.

As AbbVie used adalimumab 25 mg/mL, 0.8 mL in vial for the M06-806 pivotal clinical study, a description of the manufacturing process for the adalimumab 25 mg/mL, 0.8 mL in vial was provided along with testing results for the characterization, comparability, batch release, and stability.

There was also updated information provided for the anti-drug antibody assay. Specifically, the original ADA assay was validated at Abbott Laboratories in Ludwigshafen Germany. The assay was revalidated at the same site with slight modifications to (b) (4) (b) (4). This re-validated assay was transferred to (b) (4). The current submission contains the partial validation of the assay at (b) (4) (b) (4)

In addition, the sponsor made a change in the confirmatory ADA assay which involved (b) (4) (b) (4). The partial revalidation report for the confirmatory assay was also provided in this submission.

I found these are acceptable.

Conclusions:

I. Recommendation: **Approval from CMC perspective**

II. Sections Deferred to other reviewers: validation extension of the container closure integrity test will be reviewed by BMAB

III. Post-marketing commitments: None

IV. Future Inspection Items: None

cc:

Park/Graham	HFD-123
DMA Drive	BLA (STN: 125057/356)
DMA Paper Files	BLA (STN: 125057/356)

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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/

JUN T PARK
06/02/2014

LAURIE J GRAHAM
06/02/2014

SARAH B KENNETT
06/02/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

STATISTICAL REVIEW(S)

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

CLINICAL STUDIES

BLA #:	125057
Supplement #:	356
Drug Name:	HUMIRA® (adalimumab) weight based regimen as a subcutaneous (SC) injection
Indication(s):	Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's Disease who (b) (4)
Applicant:	AbbVie, Inc.
Date(s):	Stamp Date: August 29, 2013 PDUFA Goal Date: September 28, 2014
Review Priority:	Standard 10 Month Review Cycle with Major Amendment
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Benjamin P. Vali, M.S.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Clinical Team:	Medical Reviewer: Marjorie Dannis, M.D. Medical Team Leader: Anil Rajpal, M.D.
Project Manager:	Matthew Brancazio, Pharm.D.

Keywords: sBLA review, Clinical Studies

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1 EXECUTIVE SUMMARY

The applicant submitted the results from the M06-806 trial to support the efficacy, safety and pharmacokinetics (PK) of HUMIRA® (adalimumab) for reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's Disease (CD) who (b) (4)

In study M06-806, patients were randomized into two adalimumab dosing regimens: the high-dose group received either 40 mg of adalimumab subcutaneous (SC) every other week (EOW) (if their Week 4 body weight was greater than or equal to 40 kg) or 20 mg adalimumab SC EOW (if their Week 4 body weight was less than 40 kg); and the low-dose group which received either 20 mg adalimumab SC EOW (if their Week 4 body weight was greater than or equal to 40 kg) or 10 mg adalimumab SC EOW (if their Week 4 body weight was less than 40 kg).

There were no statistically significant differences between the adalimumab high-dose and low-dose dosing regimens in regards to the following study endpoints: clinical remission at Week 26 (38.7% vs. 28.4%); clinical remission at Week 52 (33.3% vs. 23.2%); clinical response at Week 26 (59.1% vs. 48.4%); clinical response at Week 52 (41.9% vs. 28.4%); and clinical remission at Week 26 for patients achieving Week 4 clinical response (44.0% vs. 31.3%). However, it was observed that the high-dose did trend higher relative to the low-dose in all of the aforementioned clinical remission and clinical response measures. See Section 3.2 for details.

It was also observed from the exploratory external endpoint analyses that remission rates at Weeks 26 and 52 for pediatric CD patients appeared comparable to those for adults. It should be emphasized that these external endpoint analyses were all exploratory in nature (b) (4) (b) (4). Further details are presented in Section 3.2.

Overall, the design of study M06-806 appeared adequate from a statistical perspective given the difficulties in designing this pediatric trial without a placebo control group. The applicant's corresponding analysis plan also appeared acceptable. There were no statistical review issues identified for this application that would preclude product approval. Since the study failed to show a statistical difference between the two dosing regimens, there is no formal statistical evidence confirming the proposed efficacy claims for adalimumab. However, the clinical response rates presented in this review appear to be supportive of the applicant's submitted product labeling.

2 INTRODUCTION

2.1 Overview

On August 29, 2013, AbbVie, Inc. submitted this efficacy supplement (S356) to Biologics License Application (BLA) 125057 for adalimimab for reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active CD who (b) (4)
Adalimumab, administered as a SC injection, is a recombinant human immunoglobulin (IgG1) monoclonal antibody. Effective on May 31, 2002, the applicant had initiated clinical development of adalimumab under IND 10,425 in adults with CD, and adalimumab was granted FDA approval for CD in adult patients on February 27, 2007. As a post marketing requirement (PMR) of this BLA approval, for compliance to the Pediatric Research Equity Act (PREA), further development was conducted under this IND to study pediatric CD patients of six years or older. The applicant applied and obtained (prior to the completion of the adult program) Orphan Designation for adalimumab treatment of pediatric CD patients from the Office of Orphan Products Development (OOPD) on October 19, 2006.

CD is a chronic, debilitating, and currently incurable inflammatory bowel disease (IBD) that can affect the entire digestive system as well as extraintestinal organs. The most commonly involved area of the bowel is the small bowel, particularly the distal ileum, which is involved in 70% of the cases, and often in combination with colitis that occurs in 50% of the cases. Extraintestinal manifestations can also occur, and include symptoms of joint, ocular, and hepatic inflammation. Genetic, geographic, ethnic, and environmental risk factors have all been described, but the basic etiology of the disease remains unknown. The prevalence of CD in the United States is similar to that in other western nations, and is estimated from 26 to 199 cases per 100,000 persons (i.e., a total ranging from approximately 82,000 and 627,000). The disease can affect people of any age, but the most common age of onset is in the second and third decades with a female preponderance. There are currently three other treatments being marketed for the treatment of adult CD patients in addition to adalimimab: REMICADE® (infliximab; approved in 1998); TYSABRI® (vedolizumab; approved in 2008); and CIMZIA® (certolizumab; approved in 2009).

While predominantly a disease of adults, approximately 10% to 15% of CD cases are diagnosed before adulthood, and diagnoses in early childhood are found to be rare. Despite physiologic and development differences, the presentation of CD in the pediatric population is generally similar to that seen in older patients, and is heterogeneous with regard to anatomic localization and clinical severity. Infliximab is the only treatment currently marketed for the treatment of pediatric CD patients (approved in 2006).

The general approach to the treatment of CD in children is similar to that in adults with the goals being induction and maintenance of remission, prevention of relapse and hospitalizations, improving quality of life, and avoidance of disease and drug related complications. The applicant purports that adalimumab's mechanism of action will bring about clinically meaningful changes in disease state for pediatric CD patients.

An End of Phase 2 (EOP2) meeting was held on June 1, 2006 in order to discuss the study design and endpoints of the planned phase 3 pediatric CD study (see below and in Section 3.2.1 for details) for this clinical program. On February 16, 2007, a teleconference meeting between the joint clinical/statistics teams of the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) convened to further discuss the planned phase 3 study. On April 25, 2011, a Type C advice meeting was held to review the results of the phase 3 study and to gain agreement on dosing, and the pre-sBLA meeting between the applicant and DGIEP was held on April 10, 2012 primarily for discussing the format of the sBLA submission and the major review issues associated with the application. See Table 21 in the Appendix for further comments regarding the relevant meetings under IND 10,425. On August 29, 2013, AbbVie submitted the sBLA. This is a standard review; however, the review cycle was extended due to clinical and pharmacometrics issues.

This application includes data from one completed study and one ongoing study. The clinical efficacy, safety and PK of adalimumab has been primarily evaluated in one trial studying pediatric CD patients: a phase 3, multinational, multicenter, randomized, double-blind, external-controlled, and parallel dose group study (M06-806), which serves as the single pivotal study in this clinical development program. This study's efficacy and PK data will jointly serve as the basis for the efficacy claim corresponding to pediatric patients. Supportive data are from the ongoing long-term extension study M06-807 which exclusively enrolled patients who completed study M06-806. Table 1 below presents the summary information on the single pivotal clinical trial M06-806 contained in this submission. Study M06-806 will be the focus of this sBLA review.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Patients	Patient Diagnosis	Duration of Treatment
Efficacy, Safety and PK; Phase 3	M06-806	To demonstrate safety and efficacy, and assess PK of adalimumab administered via SC injection in pediatric patients (ages 6 to 17) with moderate to severe CD	Multinational, Multicenter, Randomized, Double-blind, External-controlled, Parallel Dose group	adalimumab via SC injection; **Induction (Open-Label)** *Patients ≥ 40 kg at Week 0* 160 mg at Week 0 and 80 mg at Week 2 *Patients < 40 kg at Week 0* 80 mg at Week 0 and 40 mg at Week 2 **Maintenance (Double-Blind)** *High-Dose* 40 mg EOW (patients ≥ 40 kg at Week 4) 20 mg EOW (patients < 40 kg at Week 4) *Low-Dose* 20 mg EOW (patients ≥ 40 kg at Week 4) 10 mg EOW (patients < 40 kg at Week 4) Dosage could be adjusted at Week 26 if body weight increased to ≥ 40 kg In case of flare or non-response at Week 12, patients could switch to blinded EW dosing In case of continued flare or non-response for 8 more weeks, patients switched to open-label dosing at Week 20: 40 mg EW (patients ≥ 40 kg) 20 mg EW (patients < 40 kg)	Total: 192	Pediatric patients (ages 6 to 17) with moderate to severe CD	52 weeks

Source: Reviewer's Table.
Note: EOW = every other week; EW = every week.

2.2 Data Sources

This sBLA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Biologics Evaluation and Research (CBER) electronic document room (EDR) at the location: \\cdsesub1\evsprod\BLA125057. Sequences 0234, 0262, 0275, and 0277 contain all the contents relevant for this review.

For study M06-806, the applicant's clinical study report (CSR), clinical datasets and analysis datasets were reviewed. The clinical and analysis datasets were both in a legacy format (i.e., not compliant with any established data standards). Adequate data definition files (in Define.PDF format), a reviewer's guide and software code (in .SAS format) were also submitted for the study.

3 STATISTICAL EVALUATION

The statistical evaluation is for pivotal trial M06-806 only.

3.1 Data and Analysis Quality

This study utilized Case Report Forms (CRF), and the submitted data quality and integrity appeared to be adequate. It was possible to reproduce the primary analysis dataset (along with the numerical results presented within the CSR), specifically the primary endpoint values, from the original data source. It was possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 9.6 of their CSR. The blinding/unblinding procedures were documented within the protocol and in Section 9.4.6 of the CSR.

The original statistical analysis plan (SAP) was finalized on August 4, 2008. An amendment to the SAP, which was exclusively used to add further details regarding a conversion factor algorithm used to compare the remission rates between the pediatric patients from M06-806 and adult CD patients from trial M02-404 (which was the pivotal maintenance study from the adalimumab adult CD development program), was finalized on June 25, 2010. Further information and details regarding this conversion factor algorithm and its purpose are provided below in Sections 3.2.1 and 3.2.2.5 along with the Appendix. The SAP, along with the amendment, was submitted, and all relevant analysis decisions were made within the original SAP long before trial completion on May 18, 2010. Database hard-lock and official study unblinding were both on July 16, 2010.

3.2 Evaluation of Efficacy

3.2.1 Background, Study Design and Endpoints

Background

The original M06-806 trial protocol was finalized on December 14, 2006 after the EOP2 meeting held on June 1, 2006. The study design and endpoints for study M06-806 were discussed at the EOP2 meeting. Specific suggestions and comments made by DGIEP pertained to dosing, the inclusion of sufficient infliximab failures into the trial, the lack of a placebo control group being acceptable due to ethical reasons, and collecting additional Crohn's Disease Activity Index (CDAI) data in older patients (i.e., patients who were at least 13 years of age). These comments and suggestions were incorporated by AbbVie into the original protocol.

On October 19, 2006, a teleconference meeting between DGIEP and the applicant was held to further discuss study M06-806. During this teleconference meeting, DGIEP informed the applicant that merely comparing the proportion of remitters/responders of two dosing adalimumab regimens (see study design below) would not necessarily be interpreted as being sufficient without comparing these proportions to a control group. Because there was no placebo control group in study M06-806, DGIEP suggested that the protocol should specify that remission/response rates in the pediatric trial be compared to external remission/response rates coming from the appropriate adult CD adalimumab trials. It was thought that this external comparison could serve as additional support for determining whether children with CD could benefit from adalimumab therapy thereby boosting the level of evidence in regard to the study's clinical efficacy data. The applicant agreed to consider these additions; however, these external comparisons were not incorporated into the original protocol finalized on December 14, 2006.

On February 16, 2007, another teleconference meeting between DGIEP and the applicant was held to discuss study M06-806. Based on the conversations from the October 19, 2006 teleconference, the applicant incorporated (into the M06-806 protocol) comparisons to an external control group, specifically adult CD patients from trial M02-404, which was the pivotal maintenance study from the adalimumab adult CD development program. According to the DGIEP team, a conversion factor was necessary to more adequately compare the clinical remission rates between the pediatric patients from trial M06-806 (which utilized Pediatric Crohn's Disease Activity Index [PCDAI]) and the adult patients from trial M02-404 (which utilized CDAI). The applicant suggested certain algorithms for this conversion factor that the DGIEP team didn't disagree with, however no definitive commitment was made by DGIEP regarding the specific suggested approaches. On March 6, 2007, the M06-806 protocol was amended to add the previously discussed external comparisons using a conversion factor algorithm which was ultimately chosen by the applicant and presented within their SAP. For details regarding these external comparisons and the corresponding chosen conversion factor algorithm, please see below within this section along with Section 3.2.2.5 and the Appendix.

The M06-806 trial was subsequently started (i.e., first patient first visit) on May 4, 2007, and it concluded (i.e., last patient last visit) on May 18, 2010. The M06-806 protocol was amended four additional times since the March 6, 2007 version, and the final amendment was made on

March 30, 2010. All of the protocol amendments were either administrative in nature or contained minor changes which had no notable impact on the originally pre-specified study endpoints and corresponding analyses. Consequently this section will cover what was presented within the final M06-806 protocol finalized on March 30, 2010. Please see Table 21 in the Appendix for further comments regarding the relevant milestones during this development program. It should be noted that the design of study M06-806 was homologous to the pivotal trial, study T72, from infliximab's development program for pediatric Ulcerative Colitis (BLA 103772 / S5301).

Study Design and Endpoints

Study M06-806 was designed as a phase 3, multinational (with a total of eight participating countries), multicenter (with a total of 45 participating sites), randomized, double-blind, external-controlled, and parallel dose group trial evaluating the clinical efficacy, safety and PK of adalimumab (administered by SC injection) in pediatric CD patients. The lone study objective of trial M06-806 was to specifically demonstrate the efficacy and safety of two adalimumab dosage regimens for the induction and maintenance of clinical remission (using PCDAI; see below) in pediatric patients with moderate to severe CD while additionally assessing the PK of these two dosing regimens. The M06-806 study serves as the single pivotal study in this clinical development program as its efficacy and PK data will jointly serve as the basis for the efficacy claim corresponding to pediatric CD patients.

The patients targeted for enrollment were between the ages of six and 17 inclusive with a diagnosis of moderate to severe CD (using PCDAI) who had failed conventional therapy for CD or who had previously lost response (or had adverse reactions) to infliximab. Confirmation of CD was made by endoscopic or radiological evaluation. At least 80 of the enrolling patients were targeted to be at least 13 years of age, and between 33% and 50% of the enrolling patients were targeted to being those who had previously lost response (or had adverse reactions) to infliximab.

PCDAI was used to assess CD activity during this trial. It is an index utilized to evaluate pediatric patients within four specific areas: historical (i.e., patient reporting the degree of abdominal pain, stool pattern, and patient functioning during the previous week), physical examination (i.e., weight, height, abdomen, and perirectal disease), extraintestinal manifestations (e.g., fever, rash arthritis, and uveitis), and certain laboratory values (i.e., HCT, ESR, and serum albumin). The range of the total score is from zero to 100. Scores above 30 were considered to indicate moderate to severe CD activity which was a M06-806 inclusion criteria as stated previously. Clinical remission was defined as a PCDAI score of less than or equal to 10 points. Clinical response was defined as a decrease from baseline in PCDAI score of at least 15 points. The PCDAI score was calculated at all protocol defined visits during study M06-806; study M06-806 utilized one central laboratory for the aforementioned laboratory assessments specific to PCDAI. The details of the PCDAI Scoring System are presented in the Appendix after Table 21.

This phase 3 trial consisted of three study periods: a screening period of up to three weeks, a four-week open-label induction period, and a 48-week double-blind maintenance period. After the patient (and/or their parent/legal guardian) provided informed consent, the patient underwent

screening assessments and, if all eligibility criteria were met, entered the four week open-label induction period. The open-label induction dose was dependent on the patient's baseline body weight. If a patient's baseline body weight was greater than or equal to 40 kg, they received 160 mg and then 80 mg adalimumab SC at Weeks 0 and 2, respectively. If a patient's baseline body weight was less than 40 kg, they received 80 mg and then 40 mg adalimumab SC at Weeks 0 and 2, respectively.

At Week 4, patients were stratified according to their Week 4 responder status (yes/no; clinical response as defined as a decrease from baseline in PCDAI score of at least 15 points) and whether they had prior exposure to infliximab (yes/no), and then randomized 1:1 to one of two maintenance adalimumab treatment groups: low-dose or high−dose. Patients randomized to the high-dose group received either 40 mg of adalimumab SC EOW (if their Week 4 body weight was greater than or equal to 40 kg) or 20 mg adalimumab SC EOW (if their Week 4 body weight was less than 40 kg). Patients randomized to the low-dose group received either 20 mg adalimumab SC EOW (if their Week 4 body weight was greater than or equal to 40 kg) or 10 mg adalimumab SC EOW (if their Week 4 body weight was less than 40 kg). Note that all SC injections of study drug were administered to patients by adequately trained medical site staff at the study site during the baseline, Week 2 and Week 4 visits. Patients, if appropriate, or a designated family member were trained during these first three study visits to properly administer the study medication. Injections during subsequent visits were performed by the patient, if appropriate, or their designated family member under the supervision of the trained medical site staff in order to reinforce proper aseptic SC injection technique. Patients or their designated family member would continue to perform the SC injections in the patient's home during the weeks that they were not scheduled for clinic visits.

The randomization was conducted by a third party vendor so that AbbVie was blinded to the treatment assignments. The vendor utilized an Interactive Voice-Response System (IVRS) for the randomization. In addition, patients, Investigators, and site personnel were also blinded to the treatment assignments throughout the study until the trial was completed and the clinical database locked.

Study visits during the 48-week double-blind maintenance period were on Weeks eight, 12, 16, 20, 26, 32, 40, 48 and 52. Patient body weight was measured again at Week 26 in order to be used for readjusting the maintenance dosing regimen for patients whose body weight had increased from less than 40 kg to greater than or equal to 40 kg during the study. The site would enter a patient's body weight into the IVRS at Week 26, and the dose would be adjusted automatically (if applicable).

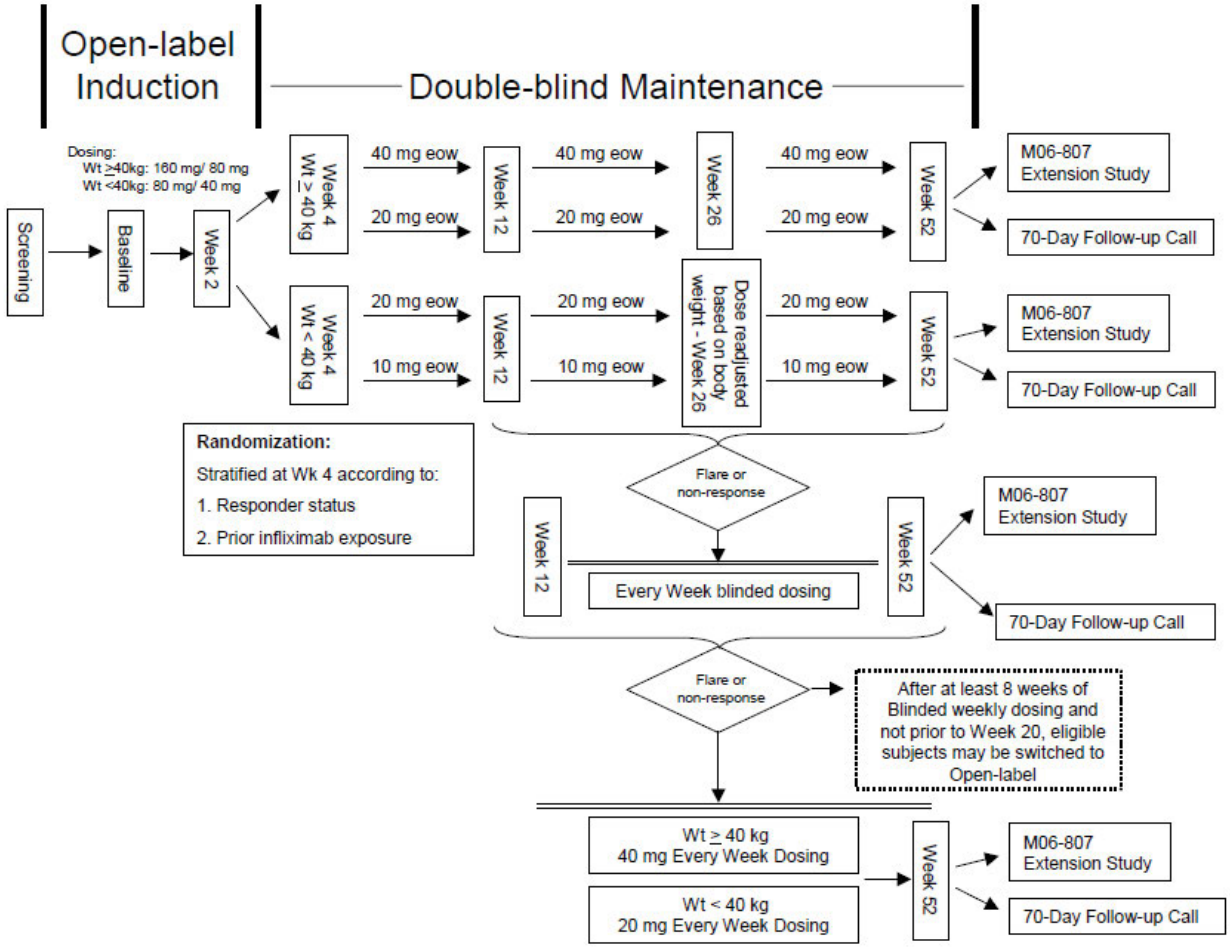
Patients were expected to remain on blinded EOW therapy throughout the 48-week double-blind maintenance period. However, starting, at the Week 12 study visit, patients who experienced a disease flare (defined as an increase in the PCDAI score of at least 15 points from Week 4, and an absolute PCDAI score above 30) or who were non-responders (defined as a decrease from baseline in PCDAI score of less than 15 points) would be dose escalated from blinded EOW dosing to blinded EW dosing while continuing with the same blinded dose.

During the blinded weekly treatment, if a patient continued to experience a flare or met the definition of non-response following an eight week course of double-blinded weekly therapy (at the earliest up to the Week 20 study visit), they would be switched to open-label weekly therapy. The dosage of this open-label weekly therapy would be 40 mg for patients with a body weight of at least 40 kg at that week (earliest being Week 20) or 20 mg for patients with a body weight of less than 40 kg at that week (earliest being Week 20). Patients receiving open-label weekly therapy that continued to have a disease flare or developed another flare would be withdrawn from the study at the investigator's discretion. In addition, patients not meeting the definition of flare but consistently not responding while receiving open-label weekly therapy would also be withdrawn from the study at the investigator's discretion.

At the conclusion of the 48-week double-blind maintenance period, patients who qualified would have the opportunity to roll over into an un-controlled, multicenter, open-label extension study, trial M06-807, in order to evaluate the long-term safety and tolerability of repeated adalimumab administration. All eligible M06-806 patients would receive open-label maintenance therapy equivalent to the M06-806 high-dose regardless of their previous M06-806 maintenance dose. At the beginning of study M06-807, patients who had dose escalated during study M06-806 would have the opportunity to dose de-escalate. Study M06-807 could continue for up to 264 weeks, which is approximately 5 years. This extension study is currently ongoing.

The full duration of study M06-806 could be up to 65 weeks, including a 10-week follow-up phone call for all patients who either terminated early from the study or who did not roll over into the M06-807 extension study. The study schema for trial M06-806 is shown below in Figure 1.

Figure 1
Study Diagram M06-806



Source: M06-806 March, 30 2010 Protocol - Figure 1 on pg. 22.

The following primary and key secondary endpoints were pre-specified by the applicant for comparing the two maintenance adalimumab dosing regimens (low-dose and high−dose). Clinical remission was defined as a PCDAI score of less than or equal to 10 points. Clinical response was defined as a decrease from baseline in PCDAI score of at least 15 points.

Primary Endpoint: Clinical remission at Week 26

Key Secondary Endpoints:

- Clinical remission at Week 52
- Clinical response at Week 26
- Clinical response at Week 52
- Clinical remission at Week 26 for patients who were clinical responders at Week 4

In addition, the following external secondary endpoints for comparing M06-806 patients to M02-404 adult patients were pre-specified by the applicant:

- Clinical remission at Week 26
- Clinical remission at Week 26 for patients who were clinical responders at Week 4
- Clinical remission at Week 4

Note that the study-wise Type I error rate was only controlled for the hypothesis testing corresponding to the internal comparisons (i.e., low-dose vs. high−dose within study M06-806). All external comparisons were outside the purview of the applicant's pre-specified multiplicity adjustment procedure, and hence were considered as exploratory analyses. Further details regarding the pre-specified multiplicity adjustment procedure are presented below in Section 3.2.2.2. Moreover, details regarding the aforementioned external comparisons and the corresponding chosen conversion factor algorithm utilized to make these comparisons are presented below in Section 3.2.2.5 and in the Appendix.

Assuming an expected clinical remission rate of 20% in the low-dose adalimumab group and 40% in the high-dose adalimumab group, a total sample size of 164 patients (that is, 82 patients per group) will provide 80% statistical power to detect the difference between the two treatment groups. This sample size calculation assumes a 1:1 randomization ratio, and it is based on a 2-sided chi-square test with a significance level of 0.05. To allow for a pre-randomization dropout rate/withdrawal rate of 10%, approximately 186 patients were expected to be enrolled (i.e., take at least the first dose of adalimumab during the four week induction period) in order to yield approximately 164 randomized patients at Week 4.

Throughout the execution of the M06-806 protocol, an Independent Data Monitoring Committee (DMC) operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. There were no formally planned interim analyses for this study.

Overall, the design of study M06-806 appeared adequate from a statistical perspective given the difficulties in designing this pediatric trial without a placebo control group. The estimated sample size was validated and confirmed as appropriate. (b) (4)

(b) (4)

Another point of emphasis pertains to the comparisons made to the external controls from the M02-404 study. Although the motivation behind these comparisons was derived from DGIEP's initial inquiries from the October, 29, 2006 teleconference, it should be affirmed that these analyses are all exploratory, and at best supportive, in nature.

During the Pre-sBLA meeting on April 10, 2012, DGIEP communicated to the applicant that these external comparisons could only be supportive in the context of the totality of data to be

submitted. See Table 21 in the Appendix for further information regarding the timeline for study M06-806 and comments pertaining to the relevant meetings under IND 10,425.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Sets

The primary analysis set, i.e., the analysis set used for all primary and secondary endpoint analyses, was the Intent-to-Treat (ITT) analysis set which included all patients randomized at Week 4 who received at least one dose of randomized study drug. In this analysis set, patients were included in the dosing group that they were randomized to receive regardless of actual dosing regimen received. This ITT analysis set was also utilized (applied to the M06-806 patients) for the external endpoint analyses as specified below in Section 3.2.2.5.

All analyses were re-conducted, for supportive analysis purposes, utilizing the Per-Protocol (PP) analysis set which included all patients in the ITT set who completed the study while being compliant with the study medication along with not having any major protocol deviations. The PP analysis set was finalized prior to database lock and study unblinding.

All analyses were again repeated, for supportive analysis purposes, utilizing an All-Randomized analysis set which included all patients randomized at Week 4. In this analysis set, patients were included in the treatment group that they were randomized to receive regardless of actual treatment received. However, because all randomized patients dosed at least once (see Table 2 below in Section 3.2.3), this analysis set was equivalent to the ITT and thus this sensitivity analysis was equivalent to the primary analysis.

3.2.2.2 Multiplicity Adjustment

In order to control the overall study-wise type I error rate, a step-down/closed sequential testing procedure was pre-specified by the applicant to adjust for the multiple comparisons on the internal study endpoints presented in the order above within Section 3.2.1. Starting with the primary endpoint, the applicant stated that the step-down could only be carried to the next endpoint, within the order presented above, if and only if the current endpoint/step was found to be statistically significant (i.e., p-value less than 0.05) in the comparison of low-dose to high-dose adalimumab. If the two adalimumab maintenance doses were not significantly different, all hypothesis testing for the subsequent internal endpoints/steps would be deemed as exploratory.

As previously stated, the study-wise Type I error rate was only controlled for the hypothesis testing corresponding to the internal comparisons (i.e., low-dose vs. high−dose within study M06-806). All external comparisons were outside the purview of the applicant's pre-specified step-down/closed sequential testing procedure, and hence are considered as exploratory analyses.

3.2.2.3 Primary Endpoint Analysis

A Cochran-Mantel-Haenszel (CMH) test was utilized for the primary endpoint analysis, adjusting for randomization strata, i.e., Week 4 response status (yes/no) and prior infliximab experience (yes/no). In order to assess the homogeneity of the response across the aforementioned strata, a Breslow-Day test at a 10% significance level was utilized. Note that the Breslow-Day test was used to supplement the CMH test and was hence exploratory in nature, i.e., its conduct was not subject to the multiplicity adjustment procedure previously described.

In addition, and for descriptive presentation purposes, two different 95% Confidence Intervals (CI) for the difference in rates between the dosing regimens were presented. The first CI was based on the normal approximation, and the second was an exact CI based on the Clopper-Pearson method.

3.2.2.4 Secondary Endpoint Analyses

The same analysis approach previously presented for the primary endpoint analysis in Section 3.2.2.3 was repeated for each key secondary endpoint analysis.

3.2.2.5 External Secondary Endpoint Analyses

Clinical Remission at Week 26

Two different external comparisons were conducted for this external analysis endpoint:

- *Comparison 1*: The percentage of M06-806 ITT patients who were in clinical remission at Week 26 based on PCDAI scores compared to the percentage of M02-404 ITT patients being administered adalimumab 40 mg EOW who were in clinical remission at Week 26 based on CDAI scores. The conversion factor algorithm was utilized for this comparison. See Appendix for details.
- *Comparison 2*: The percentage of older M06-806 ITT patients (i.e., at least 13 years of age) who were in clinical remission at Week 26 based on CDAI scores compared to the percentage of M02-404 ITT patients being administered adalimumab 40 mg EOW who were in clinical remission at Week 26 based on CDAI scores.

The adalimumab 40 mg EOW adult patients were chosen from the M02-404 study because the 40 mg EOW dosing regimen was found to be the minimally effective.

Clinical Remission at Week 26 for patients who were Clinical Responders at Week 4

Two different external comparisons were conducted for this external analysis endpoint:

- *Comparison 1*: The percentage of M06-806 ITT patients achieving clinical response at Week 4 (based on PCDAI scores) who were in clinical remission at Week 26 based on PCDAI scores compared to the percentage of M02-404 mITT patients being administered adalimumab 40 mg EOW who were in clinical remission at Week 26 based on CDAI scores. The conversion factor algorithm was utilized for this comparison. See Appendix for details.
- *Comparison 2*: The percentage of older M06-806 ITT patients (i.e., at least 13 years of age) achieving clinical response at Week 4 (based on CDAI scores) who were in clinical remission at Week 26 based on CDAI scores compared to the percentage of M02-404

mITT patients being administered adalimumab 40 mg EOW who were in clinical remission at Week 26 based on CDAI scores.

Clinical Remission at Week 4

Only one external comparison was conducted for this external analysis endpoint:

- *Comparison*: The percentage of all enrolled M06-806 patients who were in clinical remission at Week 4 based on PCDAI scores compared to the percentage of all enrolled M02-404 patients (n = 854) who were in clinical remission at Week 4 based on CDAI scores. The conversion factor algorithm was utilized for this comparison. See Appendix for details.

For the analysis of any of the previous three external endpoints, it was stated within the SAP that the applicant would claim success if the 95% CI for the difference in the percentages of interest contained zero. The applicant's justification for this conclusion within the SAP was that this result could somehow suggest equivalence between the pediatric patients in study M06-806 and adult patients from study M02-404. This conclusion, from a statistical perspective, is flawed since a CI containing zero does not in any way imply formal equivalence. And as previously stated, the fact that these external comparisons could only be, at best, supportive mitigates the impact of this error as these external analyses are considered exploratory in the end.

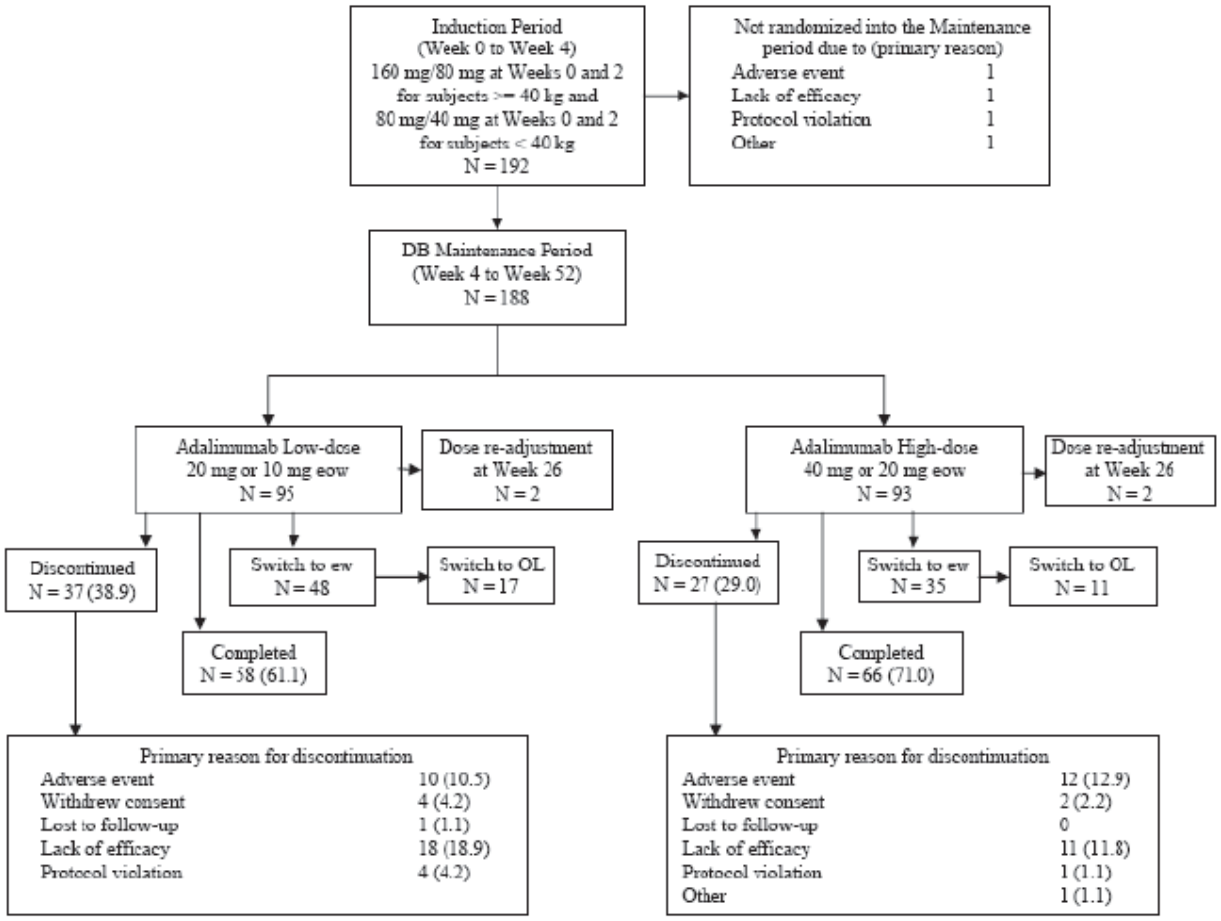
3.2.2.6 Handling of Dropouts/Missing Data

Patients from the M06-806 study who prematurely discontinued the study, or who switched from double-blind EOW dosing to double-blind EW dosing (i.e., dose escalated), or who discontinued double-blind EOW treatment before the scheduled evaluation of clinical remission, or who did not have the relevant PCDAI score (and/or CDAI score for patients greater than or equal to 13 years of age) were considered treatment failures for all of the clinical remission and clinical response analyses previously specified (i.e., those in primary, secondary and external).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all enrolled patients is displayed in Figure 3 and Table 2 below.

Figure 2
Disposition – Study M06-806



Source: M06-806 CSR - Figure 2 on pg. 205

As noted in Figure 2, in the adalimumab 20 mg/10 mg EOW (low-dose) group: 30 patients maintained their double-blind EOW dosing, and all 30 of these patients completed the study; 48 patients switched to double-blind EW dosing while 16 of these patients completed the study (32 of these patients dropped out); 17 patients switched to open-label EW dosing while 12 of these patients completed the study (5 of these patients dropped out). In the adalimumab 40 mg/20 mg EOW (high-dose) group: 47 patients maintained their double-blind EOW dosing while 41 of these patients completed the study (6 of these patients dropped out); 35 patients switched to double-blind EW dosing while 18 of these patients completed the study (17 of these patients dropped out); 11 patients switched to open-label EW dosing while 7 of these patients completed the study (4 of these patients dropped out).

Table 2
Disposition – Study M06-806
(All Enrolled Patients)

	All Randomized			
	Low-Dose 20 mg/10 mg EOW (N = 95)	High-Dose 40 mg/20 mg EOW (N = 93)	Total Randomized (N = 188)	Total Enrolled (N = 192)
All Randomized	95 (100%)	93 (100%)	188 (100%)	188 (97.9%)
Intent-to-Treat (ITT)	95 (100%)	93 (100%)	188 (100%)	188 (97.9%)
Per-Protocol (PP)	91 (95.8%)	87 (93.5%)	178 (94.7%)	178 (92.7%)
Maintained Double-Blind EOW	30 (31.2%)	47 (50.5%)	77 (41.0%)	77 (40.1%)
Completed Study	30 (31.2%)	41 (44.1%)	71 (37.8%)	71 (37.0%)
Switched to Double-Blind EW	48 (50.5%)	35 (37.6%)	83 (44.2%)	83 (43.2%)
Completed Study	16 (16.8%)	18 (19.4%)	34 (18.1%)	34 (17.7%)
Switched to Open-Label EW	17 (17.9%)	11 (11.8%)	28 (14.9%)	28 (14.6%)
Completed Study	12 (12.6%)	7 (7.5%)	19 (10.1%)	19 (9.9%)
Completed Study Overall	58 (61.1%)	66 (71.0%)	124 (66.0%)	124 (64.6%)
Discontinued Study Early	37 (38.9%)	27 (29.0%)	64 (34.0%)	64 (33.3%)
Adverse event	10 (10.5%)	12 (12.9%)	22 (11.7%)	22 (11.5%)
Withdrew consent	4 (4.2%)	2 (2.2%)	6 (3.2%)	6 (3.1%)
Lost to follow-up	1 (1.1%)	0	1 (0.5%)	1 (0.5%)
Protocol Deviation	4 (4.2%)	1 (1.1%)	5 (2.7%)	5 (2.6%)
Death	0	0	0	0
Lack of efficacy	18 (18.9%)	11 (11.8%)	29 (15.4%)	29 (15.1%)
Administrative reasons	0	0	0	0
Other	0	1 (1.1%)	1 (0.5%)	1 (0.5%)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group or overall.

The demographics, baseline, and Week 4 characteristics for all enrolled patients is presented in Table 3 below.

Table 3
Demographics, Baseline, and Week 4 Characteristics – Study M06-806
(All Enrolled Patients)

	All Randomized			
	Low-Dose 20 mg/10 mg EOW (N = 95)	High-Dose 40 mg/20 mg EOW (N = 93)	Total Randomized (N = 188)	Total Enrolled (N = 192)
Age (years)				
n	95	93	188	192
Mean (SD)	13.5 (2.47)	13.7 (2.52)	13.6 (2.49)	13.6 (2.49)
Median	14.0	14.0	14.0	14.0
Min, Max	6, 17	7, 17	6, 17	6, 17
Age Group – n (%)				
< 13 years	35 (36.8%)	31 (33.3%)	66 (35.1%)	69 (35.9%)
≥ 13 years	60 (63.2%)	62 (66.7%)	122 (64.9%)	123 (64.1%)
Gender – n (%)				
Female	41 (43.2%)	42 (45.2%)	83 (44.2%)	84 (43.8%)
Male	54 (56.8%)	51 (54.8%)	105 (55.9%)	108 (56.3%)
Race – n (%)				
Asian	0	3 (3.2%)	3 (1.6%)	3 (1.6%)
Black	6 (6.3%)	5 (5.4%)	11 (5.9%)	11 (5.7%)
Multi-Race	2 (2.1%)	1 (1.1%)	3 (1.6%)	3 (1.6%)
Other	2 (2.1%)	3 (3.2%)	5 (2.7%)	5 (2.6%)
White	85 (89.5%)	81 (87.1%)	166 (88.3%)	170 (88.5%)
Geographic Region – n (%)				
Europe	30 (31.6%)	25 (26.9%)	55 (29.3%)	55 (28.7%)
North America	65 (68.4%)	68 (73.1%)	133 (70.7%)	137 (71.4%)
Weight (kg) at Baseline				
n	95	93	188	192
Mean (SD)	44.4 (13.96)	46.3 (16.79)	45.3 (15.41)	45.1 (15.36)
Median	43.0	44.0	43.0	43.0
Min, Max	19, 81	19, 120	19, 120	19, 120
Weight Category at Baseline – n (%)				
< 40 kg	35 (36.8%)	32 (34.4%)	67 (35.6%)	69 (35.9%)
≥ 40 kg	60 (63.2%)	61 (65.6%)	121 (64.4%)	123 (64.1%)
Weight (kg) at Week 4				
n	95	93	188	NA
Mean (SD)	46.2 (13.91)	47.9 (16.84)	47.0 (15.41)	
Median	44.0	46.0	45.0	
Min, Max	20, 85	20, 122	20, 122	
Weight Category at Week 4 – n (%)				
< 40 kg	31 (32.6%)	29 (31.2%)	60 (31.9%)	NA
≥ 40 kg	64 (67.4%)	64 (68.8%)	128 (68.1%)	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group or overall. NA = not applicable (same result as under the Total Randomized column).

Table 3 - Continued
Demographics, Baseline, and Week 4 Characteristics – Study M06-806
(All Enrolled Patients)

	All Randomized			
	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)	Total Randomized (N = 188)	Total Enrolled (N = 192)
Prior Exposure to Infliximab – n (%)				
Yes	41 (43.2%)	42 (45.2%)	83 (44.2%)	85 (44.3%)
No	54 (56.8%)	51 (54.8%)	105 (55.9%)	107 (55.7%)
Clinical Response at Week 4 – n (%)				
Yes	80 (84.2%)	75 (80.6%)	155 (82.5%)	NA
No	15 (15.8%)	18 (19.4%)	33 (17.6%)	
PCDAI Score at Baseline				
n	95	93	188	192
Mean (SD)	40.8 (6.77)	41.3 (7.21)	41.1 (6.98)	40.9 (7.44)
Median	40.0	40.0	40.0	40.0
Min, Max	30, 63	25, 63	25, 63	8, 63
PCDAI Score at Week 4				
n	95	93	188	NA
Mean (SD)	17.5 (8.82)	19.7 (11.28)	18.6 (10.14)	
Median	15.0	20.0	17.5	
Min, Max	0, 45	0, 53	0, 53	
CDAI Score at Baseline				
n	60	62	122	123
Mean (SD)	243.0 (73.08)	279.3 (99.40)	261.5 (88.98)	259.9 (90.28)
Median	246.0	263.5	255.0	254.0
Min, Max	80, 432	75, 470	75, 470	70, 470
CDAI Score at Week 4				
n	60	62	122	NA
Mean (SD)	122.1 (67.66)	174.5 (113.92)	148.5 (97.11)	
Median	110.0	146.5	125.0	
Min, Max	14, 312	19, 519	14, 519	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group or overall. NA = not applicable (same result as under the Total Randomized column).

The only apparent imbalance between the dose groups corresponds to the CDAI scores at baseline and at Week 4. This is due to two outlying CDAI observations in the high-dose group. There are no other significant imbalances between the dose groups regarding the presented demographic, baseline and Week 4 characteristics.

3.2.4 Results and Conclusions

The results displayed in this section correspond to the endpoint order previously specified in Section 3.2.1 above. Note that within this review document, all the results presented in the reviewer's tables are agreeable to those reported by the applicant.

Internal Endpoints

Table 4
Clinical Remission at Week 26 – Study M06-806
(ITT)

Strata	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)	Treatment Difference (%)
Overall			[1] 10.3
Clinical Remission at Week 26			[2] (-3.14, 23.71)
Yes – n (%)	27 (28.4%)	36 (38.7%)	[3] (-4.22, 24.12)
No – n	68	57	[4] 0.0753
			[5] 0.4060
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: Yes			
Clinical Remission at Week 26			
Yes – n	7	6	
No – n	25	26	
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: No			
Clinical Remission at Week 26			
Yes – n	1	1	
No – n	8	9	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: Yes			
Clinical Remission at Week 26			
Yes – n	18	27	
No – n	30	16	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: No			
Clinical Remission at Week 26			
Yes – n	1	2	
No – n	5	6	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group.
[1]: Difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose).
[2]: 95% CI of the difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose) based on normal approximation.
[3]: Exact 95% CI of the difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose) based on Clopper-Pearson method.
[4]: P-value associated with CMH test adjusted for randomization strata, i.e., prior infliximab exposure (yes/no) and Week 4 responder status (yes/no).
[5]: P-value associated with corresponding Breslow-Day test to assess homogeneity.

It can be observed from Table 4 above that there was no significant difference between the adalimumab high-dose and low-dose and that the Week 26 remission data were homogeneous across the four strata. Due to the applicant's pre-specified multiplicity adjustment approach all subsequent hypothesis testing corresponding to the secondary endpoints which follow will be exploratory in nature. Although there was no significant difference between the two dosing regimens, it can be observed that the high-dose did trend higher relative to the low-dose in terms of the clinical remission rate at Week 26. This analysis was repeated utilizing the PP analysis set, and the conclusions were consistent. It is important to note that no single site influenced or drove the overall study results. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three for their PCDAI scores at baseline and at Week 26).

Table 5
Clinical Remission at Week 52 – Study M06-806
(ITT)

Strata	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)	Treatment Difference (%)
Overall			[1] 10.2
Clinical Remission at Week 52			[2] (-2.62, 22.97)
Yes – n (%)	22 (23.2%)	31 (33.3%)	[3] (-4.22, 24.12)
No – n	73	62	[4] 0.1004
			[5] 0.2042
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: Yes			
Clinical Remission at Week 52			
Yes – n	5	8	
No – n	27	24	
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: No			
Clinical Remission at Week 52			
Yes – n	2	0	
No – n	7	10	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: Yes			
Clinical Remission at Week 52			
Yes – n	13	20	
No – n	35	23	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: No			
Clinical Remission at Week 52			
Yes – n	2	3	
No – n	4	5	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group.
[1]: Difference in percentage of clinical remission at Week 52 (High-Dose – Low-Dose).
[2]: 95% CI of the difference in percentage of clinical remission at Week 52 (High-Dose – Low-Dose) based on normal approximation.
[3]: Exact 95% CI of the difference in percentage of clinical remission at Week 52 (High-Dose – Low-Dose) based on Clopper-Pearson method.
[4]: P-value associated with CMH test adjusted for randomization strata, i.e., prior infliximab exposure (yes/no) and Week 4 responder status (yes/no).
[5]: P-value associated with corresponding Breslow-Day test to assess homogeneity.

It can be observed from Table 5 above that the high-dose did trend higher relative to the low-dose in terms of the clinical remission rate at Week 52, and that the Week 52 remission data were homogeneous across the four strata. This analysis was repeated utilizing the PP analysis set, and the conclusions were consistent.

Table 6
Clinical Response at Week 26 – Study M06-806
(ITT)

Strata	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)	Treatment Difference (%)
Overall			[1] 10.7
Clinical Response at Week 26			[2] (-3.45, 24.89)
Yes – n (%)	46 (48.4%)	55 (59.1%)	[3] (-3.75, 25.03)
No – n	49	38	[4] 0.0732
			[5] 0.6806
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: Yes			
Clinical Response at Week 26			
Yes – n	10	18	
No – n	22	14	
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: No			
Clinical Response at Week 26			
Yes – n	2	2	
No – n	7	8	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: Yes			
Clinical Response at Week 26			
Yes – n	32	32	
No – n	16	11	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: No			
Clinical Response at Week 26			
Yes – n	2	3	
No – n	4	5	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group.
[1]: Difference in percentage of clinical response at Week 26 (High-Dose – Low-Dose).
[2]: 95% CI of the difference in percentage of clinical response at Week 26 (High-Dose – Low-Dose) based on normal approximation.
[3]: Exact 95% CI of the difference in percentage of clinical response at Week 26 (High-Dose – Low-Dose) based on Clopper-Pearson method.
[4]: P-value associated with CMH test adjusted for randomization strata, i.e., prior infliximab exposure (yes/no) and Week 4 responder status (yes/no).
[5]: P-value associated with corresponding Breslow-Day test to assess homogeneity.

It can be observed from Table 6 above that the high-dose did trend higher relative to the low-dose in terms of the clinical response rate at Week 26, and that the Week 26 response data were homogeneous across the four strata. This analysis was repeated utilizing the PP analysis set, and the conclusions were consistent.

Table 7
Clinical Response at Week 52 – Study M06-806
(ITT)

Strata	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)	Treatment Difference (%)
Overall			[1] 13.5
Clinical Response at Week 52			[2] (-0.01, 27.04)
Yes – n (%)	27 (28.4%)	39 (41.9%)	[3] (-1.02, 27.21)
No – n	68	54	[4] 0.0377
			[5] 0.4514
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: Yes			
Clinical Response at Week 52			
Yes – n	7	10	
No – n	25	22	
Prior Exposure to Infliximab: Yes			
Clinical Response at Week 4: No			
Clinical Response at Week 52			
Yes – n	2	1	
No – n	7	9	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: Yes			
Clinical Response at Week 52			
Yes – n	16	25	
No – n	32	18	
Prior Exposure to Infliximab: No			
Clinical Response at Week 4: No			
Clinical Response at Week 52			
Yes – n	2	3	
No – n	4	5	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group.
[1]: Difference in percentage of clinical response at Week 52 (High-Dose – Low-Dose).
[2]: 95% CI of the difference in percentage of clinical response at Week 52 (High-Dose – Low-Dose) based on normal approximation.
[3]: Exact 95% CI of the difference in percentage of clinical response at Week 52 (High-Dose – Low-Dose) based on Clopper-Pearson method.
[4]: P-value associated with CMH test adjusted for randomization strata, i.e., prior infliximab exposure (yes/no) and Week 4 responder status (yes/no).
[5]: P-value associated with corresponding Breslow-Day test to assess homogeneity.

It can be observed from Table 7 above that the high-dose did trend higher relative to the low-dose in terms of the clinical response rate at Week 52, and that the Week 52 response data were homogeneous across the four strata. This analysis was repeated utilizing the PP analysis set, and the conclusions were consistent.

Table 8
Clinical Remission at Week 26 for Patients Achieving Week 4 Clinical Response – Study M06-806
(ITT Patients Achieving Week 4 Clinical Response)

Strata	Low-Dose 20 mg/ 10 mg EOW (N = 80)	High-Dose 40 mg/ 20 mg EOW (N = 75)	Treatment Difference (%)
Overall			[1] 12.8
Clinical Remission at Week 26			[2] (-2.39, 27.89)
Yes – n (%)	25 (31.3%)	33 (44.0%)	[3] (-3.06, 28.21)
No – n	55	42	[4] 0.0702
			[5] 0.1024
Prior Exposure to Infliximab: Yes			
Clinical Remission at Week 26			
Yes – n	7	6	
No – n	25	26	
Prior Exposure to Infliximab: No			
Clinical Remission at Week 26			
Yes – n	18	27	
No – n	30	16	

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each dose group.
[1]: Difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose).
[2]: 95% CI of the difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose) based on normal approximation.
[3]: Exact 95% CI of the difference in percentage of clinical remission at Week 26 (High-Dose – Low-Dose) based on Clopper-Pearson method.
[4]: P-value associated with CMH test adjusted for randomization strata, i.e., prior infliximab exposure (yes/no) and Week 4 responder status (yes/no).
[5]: P-value associated with corresponding Breslow-Day test to assess homogeneity.

It can be observed from Table 8 above that the high-dose did trend higher relative to the low-dose in terms of the clinical remission rate at Week 26 for patients achieving Week 4 clinical response, and that the Week 26 remission data for these patients were homogeneous across the two strata. This analysis was repeated utilizing the PP analysis set, and the conclusions were consistent.

External Secondary Endpoints

For reference purposes, Table 9 below presents the clinical remission rates at Week 4, Week 26, and Week 52 for the 40 mg EOW ITT patients, 40 mg EOW mITT patients, and all enrolled patients from the M02-404 study. In that study, clinical remission was specifically defined as a CDAI score of less than 150.

Table 9
Clinical Remission Rates from the M02-404 Study

Time Points	40 mg EOW ITT (N = 260)	40 mg EOW mITT (N = 172)	All Enrolled Patients (N = 854)
Clinical Remission at Week 4			
Yes – n (%)	81 (31.2%)	81 (47.1%)	216 (25.3%)
No – n	179	91	638
Clinical Remission at Week 26			
Yes – n (%)	87 (33.5%)	68 (39.5%)	205 (24.0%)
No – n	173	104	649
Clinical Remission at Week 52			
Yes – n (%)	76 (29.2%)	62 (36.0%)	181 (21.2%)
No – n	184	110	673

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients in each analysis set or overall.

Tables 10, 11, and 12, respectively, present the results from the pre-specified external secondary endpoint analyses: clinical remission at Week 26; clinical remission at Week 26 for patients who were clinical responders at Week 4; and clinical remission at Week 4.

Table 10
External Analysis of Clinical Remission at Week 26

	Step 1			*Step 2*		*Step 3*			
Treatment	CDAI Remission Rate (X) n/N (%)	PCDAI Remission Rate (Y) n/N (%)	Conversion Factor (CF = X/Y)	M06-806 ITT PCDAI Remission Rate (Z) [1] n/N (%)	Adjusted M06-806 ITT PCDAI Remission Rate (CF × Z)	M02-404 ITT 40 mg EOW CDAI Remission Rate [2] n/N (%)	Difference (Δ) [3]	***Comparison 1*: 95% CI for Δ (%)**	***Comparison 2*: Δ and 95% CI [4] (%)**
Overall	62/122 (50.8%)	45/122 (36.9%)	1.38	63/188 (33.5%)	46.2%	87/260 (33.5%)	12.7%	**(3.56, 21.86)**	**17.3% (6.74, 27 86)**
Low-Dose	33/60 (55.0%)	21/60 (35.0%)	1.57	27/95 (28.4%)	44.6%	87/260 (33.5%)	11.1%	**(-0.33, 22.73)**	**21.5% (7.67, 35 33)**
High-Dose	29/62 (46.8%)	24/62 (38.7%)	1.21	36/93 (38.7%)	46.8%	87/260 (33.5%)	13.3%	**(1.66, 24.96)**	**13.3% (-0.38, 26.98)**

Source: Reviewer's Table.
Note: Reminder that *Step 1* data was generated exclusively from M06-806 ITT patients who were at least 13 years of age.
[1] Data directly from, or derived from, Table 4 above.
[2] Data from Table 9 above.
[3] Difference is between the adjusted M06-806 ITT PCDAI remission rate and the M02-404 ITT 40 mg EOW CDAI remission rate.
[4] 95% CI of the difference (denoted as Δ) between the M06-806 ITT CDAI remission rate in older patients (i.e., at least 13 years of age; first column of *Step 1* in this table) and the M02-404 ITT 40 mg EOW CDAI remission rate.

Table 11
External Analysis of Clinical Remission at Week 26 for Patients Achieving Week 4 Clinical Response

	Step 1			*Step 2*		*Step 3*			
Treatment	CDAI Remission Rate (X) n/N (%)	PCDAI Remission Rate (Y) n/N (%)	Conversion Factor (CF = X/Y)	M06-806 ITT PCDAI Remission Rate (Z) [1] n/N (%)	Adjusted M06-806 ITT PCDAI Remission Rate (CF × Z)	M02-404 mITT 40 mg EOW CDAI Remission Rate [2] n/N (%)	Difference (Δ) [3]	***Comparison 1*: 95% CI for Δ (%)**	***Comparison 2*: Δ and 95% CI [4] (%)**
Overall	57/100 (57.0%)	41/100 (41.0%)	1.39	58/155 (37.4%)	52.0%	68/172 (39.5%)	12.5%	**(1.75, 23.22)**	**17.5% (5.35, 29.65)**
Low-Dose	30/51 (58.8%)	19/51 (37.3%)	1.58	25/80 (31.3%)	49.5%	68/172 (39.5%)	10.0%	**(-3.36, 22.98)**	**19.3% (3.94, 34.66)**
High-Dose	27/49 (55.1%)	22/49 (44.9%)	1.23	33/75 (44.0%)	54.1%	68/172 (39.5%)	14.6%	**(1.03, 27.90)**	**15.6% (-0.13, 31.33)**

Source: Reviewer's Table.
Note: Reminder that *Step 1* data was generated exclusively from M06-806 ITT patients who were at least 13 years of age.
[1] Data directly from, or derived from, Table 8 above.
[2] Data from Table 9 above.
[3] Difference is between the adjusted M06-806 ITT PCDAI remission rate and the M02-404 mITT 40 mg EOW CDAI remission rate.
[4] 95% CI of the difference (denoted as Δ) between the M06-806 ITT CDAI remission rate in older patients (i.e., at least 13 years of age; first column of *Step 1* in this table) and the M02-404 mITT 40 mg EOW CDAI remission rate.

Table 12
External Analysis of Clinical Remission at Week 4

	Step 1			*Step 2*		*Step 3*			
Treatment	CDAI Remission Rate (X) n/N (%)	PCDAI Remission Rate (Y) n/N (%)	Conversion Factor (CF = X/Y)	All Enrolled M06-806 PCDAI Remission Rate (Z) n/N (%)	Adjusted All Enrolled M06-806 PCDAI Remission Rate (CF × Z)	All Enrolled M02-404 CDAI Remission Rate [1] n/N (%)	Difference (Δ) [2]	***Comparison 1*: 95% CI for Δ (%)**	***Comparison 2*: Δ and 95% CI [3] (%)**
Overall	76/123 (61.8%)	37/123 (30.1%)	2.05	52/192 (27.1%)	55.6%	216/854 (25.3%)	30.3%	**(22.73, 37 95)**	**36.5% (27.43, 45.57)**

Source: Reviewer's Table.
Note: Reminder that *Step 1* data was generated exclusively from all enrolled M06-806 patients who were at least 13 years of age.
[1] Data from Table 9 above.
[2] Difference is between the adjusted all enrolled M06-806 PCDAI remission rate and the all enrolled M02-404 CDAI remission rate.
[3] 95% CI of the difference (denoted as Δ) between the M06-806 CDAI remission rate in all enrolled older patients (i.e., at least 13 years of age; first column of *Step 1* in this table) and the all enrolled M02-404 CDAI remission rate.

It can be observed from Tables 10 and 11 (which present results from the clinical remission at Week 26 and clinical remission at Week 26 for patients who were clinical responders at Week 4 analyses, respectively), that adalimimab in pediatric CD patients overall appeared to be more efficacious than adalimimab in adult CD patients. Although the results were mixed when analyzed by individual dosing regimens, they might suggest that the remission rates are similar between the adalimimab pediatric CD patients and their counterparts from the adalimimab adult CD development program. It can be observed from Table 12 (which presents results from the clinical remission at Week 4 analysis) that the induction dose from study M06-806 might be more efficacious than that utilized in study M02-404. However, it should again be emphasized that these analyses were all exploratory in nature, (b) (4)

(b) (4)

(b) (4)

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As stated previously in Section 3.2.1, at the conclusion of the 48-week double-blind maintenance period in study M06-806, patients who qualified would have the opportunity to roll over into long-term extension study M06-807. In the end, out of the 188 patients randomized into the M06-806 study, 100 participated in study M06-807. Table 13 below displays the long term PCDAI clinical remission and clinical response rates over time. This table presents observed cases, i.e., the denominator at each time point represents the total number of patients who had currently been on study through that time point. Note that for the clinical response rate calculations, the baseline value was from the M06-806 baseline/Week 0 visit. This study is currently ongoing.

Table 13
Clinical Remission and Clinical Response Over Time – Study M06-807
(All Enrolled)

Study M06-807 Visit	PCDAI Clinical Remission [1] n/N (%)	PCDAI Clinical Response [2] n/N (%)
Week 0	67/100 (67.0%)	95/100 (95.0%)
Week 4	65/98 (66.3%)	90/98 (91.8%)
Week 8	67/96 (69.8%)	91/96 (94.8%)
Week 12	60/96 (62.5%)	87/96 (90.6%)
Week 24	59/94 (62.8%)	88/94 (93.6%)
Week 36	61/89 (68.5%)	83/89 (93.3%)
Week 48	55/83 (66.3%)	75/83 (90.4%)
Week 60	62/82 (75.6%)	79/82 (96.3%)
Week 72	45/68 (66.2%)	65/68 (95.6%)
Week 84	36/48 (75.0%)	45/48 (93.8%)
Week 96	30/38 (78.9%)	36/38 (94.7%)
Week 108	21/29 (72.4%)	29/29 (100%)
Week 120	12/15 (80.0%)	15/15 (100%)
Week 144	3/3 (100%)	3/3 (100%)

Source: Reviewer's Table.
Note: Denominators for percentages are N, the number of patients who had currently been on study through that time point. Data cutoff was July 31, 2011.
[1]: Clinical remission defined as PCDAI score less than or equal to 10 points.
[2]: Clinical response defined as a decrease from study M06-806 baseline in PCDAI score of at least 15 points.

It can be observed from Table 13 that the clinical remission and clinical response rates were reasonably maintained through Week 96 by the cohort of patients rolling over from study M06-806. The data began to get sparse after Week 96; the final results from the fully completed study are needed to properly adjudicate the durability of clinical remission and clinical response.

3.3 Evaluation of Safety

Adalimumab appeared to be generally safe and well-tolerated in pediatric subjects with moderate to severe CD. No deaths occurred during study M06-806 or M06-807. There were no

malignancies, demyelinating diseases or tuberculosis, and serious adverse events (SAEs) were experienced by 22% of the patients overall. The most frequently reported treatment-emergent adverse events (TEAEs), occurring in at least 10% of the patients, were headache, nausea, upper respiratory tract infection, nasopharyngitis, pyrexia, oropharyngeal pain, diarrhea, vomiting, injection site reaction, and abdominal pain. The incident rates for TEAEs and SAEs were almost equal between the high-dose and low-dose groups. In conclusion, the two dosing regimens were very similar in regards to safety. Please see Section 7 of the clinical review for the full details regarding the safety profile of adalimumab in pediatric patients.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented in this section correspond to the primary endpoint of study M06-806 (i.e., clinical remission at Week 26).

4.1 Gender, Race, Age, and Geographic Region

The gender subgroup analysis results are presented in Table 14 below. It was found that the results were consistent across the gender subgroups**,** and consistent with the overall population as seen in Table 4 above.

Table 14
Clinical Remission at Week 26 by Gender – Study M06-806
(ITT)

Gender Subgroup	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
Female		
Clinical Remission at Week 26 – *n*	41	42
Yes – n (%)	13 (31.7%)	17 (40.5%)
No – n	28	25
Male		
Clinical Remission at Week 26 – *n*	54	51
Yes – n (%)	14 (25.9%)	19 (37.3%)
No – n	40	32

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

The race subgroup analysis results are presented in Table 15 below. It should be noted that due to small sample sizes, the Asian, Black, Multi-Race, and Other race groups were pooled into a single race group called 'Non-White'. It was found that the 'Non-White' subgroup was still too sparse in size for analysis. The results from the 'White' subgroup were consistent with the overall population as seen in Table 4 above.

Table 15
Clinical Remission at Week 26 by Race – Study M06-806
(ITT)

Race Subgroup	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
Non-White		
Clinical Remission at Week 26 – *n*	10	12
Yes – n (%)	1 (10.0%)	5 (41.7%)
No – n	9	7
White		
Clinical Remission at Week 26 – *n*	85	81
Yes – n (%)	26 (30.6%)	31 (38.3%)
No – n	59	50

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

The age subgroup analysis results are presented in Table 16 below. It was found that the results were reasonably consistent across the age subgroups (with the lone exception being low-dose patients less than 13 years old), and reasonably consistent with the overall population as seen in Table 4 above.

Table 16
Clinical Remission at Week 26 by Age – Study M06-806
(ITT)

Age Subgroup	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
< 13 years old		
Clinical Remission at Week 26 – *n*	35	31
Yes – n (%)	6 (17.1%)	12 (38.7%)
No – n	29	19
≥ 13 years old		
Clinical Remission at Week 26 – *n*	60	62
Yes – n (%)	21 (35.0%)	24 (38.7%)
No – n	39	38

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

The geographic region subgroup analysis results are presented in Table 17 below. It was found that the results were reasonably consistent across the geographic region subgroups (with the lone

exception being high-dose patients from the European Union), and reasonably consistent with the overall population as seen in Table 4 above.

Table 17
Clinical Remission at Week 26 by Geographic Region – Study M06-806
(ITT)

Geographic Region	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
European Union		
Clinical Remission at Week 26 – *n*	30	25
Yes – n (%)	7 (23.3%)	13 (52.0%)
No – n	23	12
North America		
Clinical Remission at Week 26 – *n*	65	68
Yes – n (%)	20 (30.8%)	23 (33.8%)
No – n	45	45

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

4.2 Other Special/Subgroup Populations

There were three special subgroup populations of interest: prior infliximab exposure, clinical response at Week 4, and body weight at Week 4. The prior infliximab exposure subgroup analysis results are presented in Table 18 below. It was found that the results were inconsistent across the prior infliximab exposure subgroups as patients with prior exposure performed markedly worse than those without prior exposure.

Table 18
Clinical Remission at Week 26 by Prior Infliximab Exposure – Study M06-806 (ITT)

Prior Infliximab Exposure	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
Yes		
Clinical Remission at Week 26 – *n*	41	42
Yes – n (%)	8 (19.5%)	7 (16.7%)
No – n	33	35
No		
Clinical Remission at Week 26 – *n*	54	51
Yes – n (%)	19 (35.2%)	29 (56.9%)
No – n	35	22

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

The Week 4 clinical response subgroup analysis results are presented in Table 19 below. It was found that the results were inconsistent across the Week 4 clinical response subgroups as patients with Week 4 clinical response performed markedly better than those without Week 4 clinical response.

Table 19
Clinical Remission at Week 26 by Week 4 Clinical Response – Study M06-806 (ITT)

Clinical Response at Week 4	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
Yes		
Clinical Remission at Week 26 – *n*	80	75
Yes – n (%)	25 (31.3%)	33 (44.0%)
No – n	55	42
No		
Clinical Remission at Week 26 – *n*	15	18
Yes – n (%)	2 (13.3%)	3 (16.7%)
No – n	13	15

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

The Week 4 bodyweight subgroup analysis results are presented in Table 20 below. It was found that the results were reasonably consistent across the Week 4 bodyweight subgroups (with the

lone exception being low-dose patients less than 40 kg of bodyweight), and reasonably consistent with the overall population as seen in Table 4 above.

Table 20
Clinical Remission at Week 26 by Week 4 Bodyweight – Study M06-806
(ITT)

Bodyweight at Week 4	Low-Dose 20 mg/ 10 mg EOW (N = 95)	High-Dose 40 mg/ 20 mg EOW (N = 93)
< 40 kg		
Clinical Remission at Week 26 – *n*	31	29
Yes – n (%)	6 (19.4%)	10 (34.5%)
No – n	25	19
≥ 40 kg		
Clinical Remission at Week 26 – *n*	64	64
Yes – n (%)	21 (32.8%)	26 (40.6%)
No – n	43	38

Source: Reviewer's Table.
Note: Denominators for percentages are *n*.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Overall, the design of study M06-806 appeared adequate from a statistical perspective given the difficulties in designing this pediatric trial without a placebo control group. The applicant's corresponding analysis plan also appeared acceptable. There were no statistical review issues identified for this application that would preclude product approval.

5.2 Collective Evidence

The applicant submitted the results from the M06-806 trial to support the efficacy, safety and PK of adalimumab for the treatment of CD in pediatric patients. There was no statistically significant difference between the adalimumab high-dose and low-dose dosing regimens in regards to the following study endpoints: clinical remission at Week 26; clinical remission at Week 52; clinical response at Week 26; clinical response at Week 52; and clinical remission at Week 26 for patients achieving Week 4 clinical response. Although there was no statistically significant difference between these two dosing regimens, it was observed that the high-dose did trend higher relative to the low-dose in all of the aforementioned clinical remission and clinical response measures.

It should be noted that patients who experienced flare or inadequate response at Week 12 were not re-randomized. (b) (4)

It was also observed from the exploratory external endpoint analyses that remission rates at Weeks 26 and 52 for pediatric CD patients appeared comparable to those for adults. It should be emphasized that these external endpoint analyses were all exploratory in nature (b) (4) (b) (4)

5.3 Conclusions and Recommendations

As the study failed to show a statistical difference between the two dosing regimens, there is no formal statistical evidence confirming the proposed efficacy claims for adalimumab. However, from a statistical perspective, the clinical response rates presented in this review appear to be supportive of efficacy.

6 APPENDIX

Table 21
Timeline and Comments for Study M06-806 and Relevant Meetings under IND 10,425
(Note: Read this table starting from the upper left side down to the lower right side.)

Milestone	**1. June 1, 2006** EOP2 Meeting	**2. October 19, 2006** Teleconference to discuss M06-806	**3. December 14, 2006** Original M06-806 Protocol Finalized	**4. February 16, 2007** Teleconference to discuss M06-806
Comment (if necessary)	Study design and endpoints were discussed for the M06-806 trial. Specific suggestions and comments by DGIEP pertained to dosing, the inclusion of sufficient infliximab failures into the trial, the lack of a placebo control group being acceptable due to ethical reasons, and collecting CDAI in older patients.	During this small teleconference meeting, DGIEP informed the applicant that merely comparing the proportion of remitters/responders of two dosing adalimumab regimens would not necessarily be interpreted as being sufficient without comparing these proportions to a control group. Because there was no placebo control group in study M06-806, DGIEP suggested that the protocol should specify that remission/response rates in the pediatric trial be compared to external remission/response rates from the appropriate adult CD trials. It was thought that this external comparison could serve as additional support for determining whether children with CD could benefit from adalimumab therapy thereby boosting the level of evidence in regard to the study's clinical efficacy data.		This small teleconference meeting was held to further discuss study M06-806. Based on the conversations from the October 19, 2006 teleconference, the applicant incorporated (into the M06-806 protocol) comparisons to an external control group, specifically adult CD patients from trial M02-404, which was the pivotal maintenance study from the adalimumab adult CD development program. According to the DGIEP team, a conversion factor was necessary to more adequately compare the clinical remission rates between the pediatric patients from trial M06-806 (which utilized PCDAI) and the adult patients from trial M02-404 (which utilized CDAI). The applicant suggested certain algorithms for this conversion factor that the DGIEP team didn't disagree with, however no definitive commitment was made by DGIEP regarding the specific suggested approaches.

Table 21 (continued)

Milestone	**5. March 6, 2007** Amendment One of M06-806 Protocol	**6. May 4, 2007** M06-806 Initiated	**7. August 4, 2008** Original M06-806 SAP Finalized	**8. March 30, 2010** Final Amendment of M06-806 Protocol
Comment (if necessary)	This amendment added external comparisons between the proportion of pediatric remitters from trial M06-806 and the proportion of adult remitters from trial M02-404 using a conversion factor algorithm which was ultimately chosen by the applicant and presented within their SAP.			This was the fifth and final amendment to the protocol, and there were no major changes; the changes were primarily administrative in nature.

Milestone	**9. May 18, 2010** M06-806 Completed	**10. June 25, 2010** Final M06-806 SAP Finalized	**11. July 16, 2010** Database Hard-Lock and Unblinding for M06-806	**12. April 25, 2011** Type C Advice Meeting (Teleconference)
Comment (if necessary)		Added further details regarding the conversion factor algorithm used to compare the remission rates between the pediatric patients from M06-806 and adult CD patients from trial M02-404. All relevant analysis decisions remained unchanged.		The purpose of this teleconference meeting was to review the results of study M06-806, gain agreement on the dosing of pediatric CD patients, and to discuss sBLA submission strategy. DGIEP's most relevant comment pertained to the fact that modeling and simulation data from M06-806 along with clinical data from M06-806 would be required to support the proposed dosing. (b) (4)

Table 21 (continued)

Milestone	**13. April 10, 2012** Pre-sBLA Meeting
Comment (if necessary)	(b) (4) [redacted]
	In addition, DGIEP stated that the external comparison between the proportion of pediatric remitters from trial M06-806 and the proportion of adult remitters from trial M02-404 could be supportive in the context of the totality of data to be submitted.

Source: Reviewer's Table.

The PCDAI Scoring System

		Score
1. Abdominal pain rating		
- None	= 0 p	
- Mild - Brief, does not interfere with activities	= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal	= 10 p	
2. Stools (per day)		
- 0 – 1 liquid stools, no blood	= 0 p	
- Up to 2 semi-formed with small blood, or 2 – 5 liquid	= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	= 10 p	
3. Patient Functioning, General Well-Being		
- No limitation of activities, well	= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par	= 5 p	
- Frequent limitation of activity, very poor	= 10 p	

LABORATORY		Score
4. HCT: Male and female ≤ 10 years:	Male 11 – 14 years:	
≥ 33 = 0 p	≥ 35 = 0 p	
28 – 32 = 2.5 p	30 – 34 = 2.5 p	
< 28 = 5 p	< 30 = 5 p	
Female 11 – 19 years: ≥ 34 = 0 p	Male 15 – 19 years: ≥ 37 = 0 p	
29 – 33 = 2.5 p	32 – 36 = 2.5 p	
< 29 = 5 p	< 32 = 5 p	
5. ESR (mm/hr) < 20 = 0 p		
20 – 50 = 2.5 p		
> 50 = 5 p		
6. Albumin (g/dL) ≥ 3.5 = 0 p		
3.1 – 3.4 = 5 p		
≤ 3.0 = 10 p		

EXAMINATION		Score
7. Weight - Weight gain or voluntary weight stable/loss	= 0 p	
- Involuntary weight stable, weight loss 1% – 9%	= 5 p	
- Weight loss ≥ 10%	= 10 p	

The PCDAI Scoring System (continued)

8. Height	At Diagnosis:	Follow-up:	
	< 1 channel decrease = 0 p	Height velocity ≥ –1SD	= 0 p
	≥ 1, < 2 channel decrease = 5 p	Height velocity < –1SD, > –2SD	= 5 p
	≥ 2 channel decrease = 10 p	Height velocity ≤ –2SD	= 10 p
9. Abdomen	- No tenderness, no mass		= 0 p
	- Tenderness, or mass without tenderness		= 5 p
	- Tenderness, involuntary guarding, definite mass		= 10 p
10. Perirectal disease	- None, asymptomatic tags		= 0 p
	- 1 – 2 indolent fistula, scant drainage, no tenderness		= 5 p
	- Active fistula, drainage, tenderness, or abscess		= 10 p
11. Extra-intestinal Manifestations			
(Fever ≥ 38.5 for 3 days over past week, definite arthritis, uveitis, *E. nodosum*, *P. gangrenosum*)			= 0 p
- None			= 5 p
- One			= 10 p
- ≥ Two			
TOTAL SCORE	**Pediatric Crohn's Disease Activity Index (PCDAI)**		

Source: Table 6 on pages 154-155 of the M06-806 CSR.
Note: SD = Standard Deviation; p = points.

Conversion Factor Algorithm

According to the SAP, study M06-806's external analysis for an endpoint of interest (e.g., clinical remission at Week 26) would be considered successful by the applicant if the 95% CI for the difference between the Week 26 pediatric remission rate (based on PCDAI) and the Week 26 adult remission rate (based on CDAI; using M02-404 ITT patients administered adalimumab 40 mg EOW therapy) contained zero or if the lower bound of this CI was greater than zero. The following steps were followed to compare the results between the pediatric and adult studies.

Step 1:
For all M06-806 ITT patients who were at least 13 years old at baseline (expected at least 80 enrolled patients as previously stated in Section 3.2.1), the following was calculated:

- The percentage of patients in CDAI clinical remission (i.e., CDAI less than 150) at Week 26. Call it X. For example, X = 40%.
- The percentage of patients in PCDAI clinical remission (i.e., PCDAI less than or equal to 10) at Week 26. Call it Y. For example, Y = 22%.
- The ratio X/Y defined the conversion factor (denoted as CF). For example: CF = X/Y = (40%)/(22%) = 1.8.

Step 1 was additionally performed, and separately, for the following sets of patients:

1) All M06-806 ITT patients at least 13 years old at baseline who were randomized at Week 4 to adalimumab low-dose
2) All M06-806 ITT patients at least 13 years old at baseline who were randomized at Week 4 to adalimumab high-dose

Step 2:
The three conversion factor values (one for each set of patients previously described) determined in Step 1 were used to adjust the observed percentage of clinical remission at Week 26 (based on PCDAI) determined for ITT patients in study M06-806 to a result that could be more adequately comparable to the percentage of clinical remission at Week 26 (based on CDAI) from adult study M02-404. Specifically:

- The conversion factor value derived from all M06-806 ITT patients at least 13 years old at baseline was used to adjust the percentage of clinical remission at Week 26 (based on PCDAI) for all ITT patients in study M06-806.
  For example (continuing to use the same example numbers from above), suppose the observed percentage of clinical remission at Week 26 (based on PCDAI) for all ITT patients in study M06-806 was 25%. Call it Z, hence Z = 25%. Then the adjusted percentage of clinical remission at Week 26 would be obtained as: CF × (observed percentage of clinical remission at Week 26 based on PCDAI) = CF × Z = 1.8 × 25% = 45%.
- The conversion factor value derived from all M06-806 ITT patients at least 13 years old at baseline who were randomized at Week 4 to adalimumab low-dose was used to adjust the percentage of clinical remission at Week 26 (based on PCDAI) for all M06-806 ITT patients randomized at Week 4 to the low-dose.
- The conversion factor value derived from all M06-806 ITT patients at least 13 years old at baseline who were randomized at Week 4 to adalimumab high-dose was used to adjust

the percentage of clinical remission at Week 26 (based on PCDAI) for all M06-806 ITT patients randomized at Week 4 to the high-dose.

Step 3:
Separately for each of the three previously described set of patients, the following was performed:

- A 95% CI was calculated for the difference in proportions (presented as a percentage and denoted as Δ), using the normal approximation, between the adjusted PCDAI clinical remission at Week 26 for the M06-806 ITT patients of interest and the CDAI clinical remission at Week 26 for the M02-404 ITT patients receiving adalimumab 40 mg EOW. The CDAI clinical remission rate at Week 26 for the M02-404 ITT patients receiving adalimumab 40 mg EOW was 33.5% (see Table 9 below in Section 3.2.4). Continuing to use the data from the above example, we obtain the difference in percentages: Δ adjusted PCDAI remission rate at Week 26 – adult CDAI remission rate at Week 26 = 45% – 33.5% = 11.5%. A 95% CI around this difference would be (–0.83%, 23.82%). Note that for this example, the standard error of the adjusted PCDAI remission rate at Week 26 was calculated based on the projected number of M06-806 patients who were at least 13 years old, i.e., 80.
- It was determined whether the 95% CI contained zero or if the lower bound of the CI was greater than zero.

In the previous example, the 95% CI (–0.83%, 23.82%) does contain zero, and hence the applicant, based on the SAP, would claim success for the external analysis of this endpoint (see below regarding reviewer comment pertaining to this conclusion). Note that the standard error of the adjusted PCDAI remission rate at Week 26 would be calculated using the total number of patients in each group of interest (with the above example being all enrolled M06-806 patients who were at least 13 years old at baseline).

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/s/

BEHRANG VALI
08/29/2014

MICHAEL E WELCH
08/29/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 28 May 2014

To: Administrative File, STN 125057/356

From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB

Through: Patricia Hughes, Ph.D., Team Leader, OC/OMPQ/DGMPA/BMAB

Subject: Review of a PAS efficacy supplement proposing a new indication: pediatric Crohn's disease

US License: 1889

Applicant: AbbVie, Inc.

Facilities: (b) (4)

Product: Humira (adalimumab)

Dosage: Injectable solution in prefilled syringes (10 mg/0.2 mL) for subcutaneous injection

Indication: Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4)

Due date: 28 September 2014

Recommendation for Approvability: Efficacy supplement 125057/356 is recommended for approval from a sterility assurance and microbiology product quality perspective.

Review Summary

AbbVie, Inc. has submitted this efficacy supplement to provide for a new indication for Humira and a newly developed 10 mg/0.2 mL PFS; the formulation and container closure of the new presentation is identical to the approved Humira presentations.

The supplement was submitted in eCTD format on August 29, 2013 under sequence #0234 and it consists of documents under modules 1, 2, 3, and 5. Only drug-product sterility assurance for the prefilled syringe is reviewed here.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Conclusion

I. The supplement was reviewed from a sterility assurance perspective and microbiology product quality perspective and is recommended for approval.

II. The non-microbial aspects of this supplement should be reviewed by OBP/DMA.

III. A consult request was sent to CDRH/OC for [redacted] (b) (4). Refer to TB-EER for current GMP status of the facilities.

STN 125057/356 Microbial Quality Information Request for AbbVie, Inc. (February 21, 2014)

1. Clarify if endotoxin testing is conducted [redacted (b) (4)].
2. Movement of the stopper due to bubble expansion/contraction at worst-case pressure during air shipment may compromise sterility of the drug product by displacing the stopper to the non-sterile part of the syringe and returning it back to the original position at atmospheric pressure. Indicate if you have conducted studies demonstrating that stopper movements during air shipment of the 10 mg/0.2 mL-filled PFS does not compromise drug product sterility and submit results.
3. [redacted (b) (4)]
4.

STN 125057/356 Microbial Quality Information Request for AbbVie, Inc. (April 30, 2014)

Validate the [redacted (b) (4)] used for the 10 mg/0.2 mL PFS [redacted (b) (4)] with the [redacted (b) (4)] mm [redacted (b) (4)] and submit summary validation report.

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/s/

REYES CANDAU-CHACON
05/29/2014

PATRICIA F HUGHES TROOST
05/30/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

Submission	**STN 125057/S356**
Submission Date	**August 28, 2013**
Generic Name	**Adalimumab**
Primary Reviewers	**Jee Eun Lee, Ph.D., Jie Wang, Ph.D.**
Secondary Reviewers	**Yow-Ming Wang, Ph.D., Nitin Mehrotra, Ph.D.**
OCPB Division	**DCP3/ DPM**
ORM division	**OND/ ODE3/DGIEP**
Applicant	**Abbvie**
Formulation; Strength(s)	**50 mg/mL concentration of adalimumab pre-filled syringe (PFS) for SC injection**
Proposed Indication	**Crohn's disease in pediatric patients ≥ 6 years of age**
Proposed Dosing Regimen	• **Body Weight 17 – 40 kg** **Initial dose (Day 1) is 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose as following:** ○ (b) (4) **20 mg every other week** ○ (b) (4) (b) (4) • **Body weight ≥ 40 kg** **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 40 mg injections in one day) two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose as following:** ○ (b) (4) **40 mg every other week** ○ (b) (4) (b) (4) (b) (4)

1 EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology, Divisions of Pharmacometrics (OCP/DPM) and Clinical Pharmacology 3 (OCP/DCP 3), have reviewed the information provided in the submission and consider that the data are acceptable for supporting the approval of adalimumab for the treatment of pediatrics patients 6 years and older with Crohn's disease. Detailed dose recommendations are provided in the table below:

Body Weight	Induction Phase	Maintenance Phase
≥ 40 kg	160 mg at Week 0 followed by 80 mg at Week 2	40 mg every other week (EOW)
< 40 kg	80 mg at week 0 followed by 40 mg at week 2	20 mg EOW

- (b) (4)
-

Labeling

We have labeling recommendations for dosing regimen, pharmacokinetics, and immunogenicity (see Section 3).

1.2 Summary of Clinical Pharmacology Findings

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor-alpha (TNFα). HUMIRA® was initially approved for the treatment of rheumatoid arthritis (RA) in December 2002 and subsequently approved for multiple indications, including for the treatment of adult Crohn's Disease (CD) in February 2007. Humira has been approved for the treatment of Juvenile idiopathic arthritis (JIA) in pediatric patients with ≥ 4 years of age. The approved dosing regimen is

20 mg EOW for pediatric patients with body weight 15-30 kg and 40 mg for patients with body weight ≥ 30 kg.

The applicant conducted studies in pediatric CD subjects 6 years of age and older to fulfill a post-marketing commitment (PMC#1) following the approval of the adult CD indication. The Agency waived the pediatric study requirement for ages 0 to less than 6 years. The proposed indications of the current application are for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who (b) (4) (b) (4)

The approved dosing regimen for treatment of CD in adults is initial dose of 160 mg followed by 80 mg 2 weeks later, 40 mg 2 weeks later, and then 40 mg EOW maintenance dosing regimen. In a pivotal Phase 3 trial in adults (Study M02-404), patients were randomized to 40 mg EOW dosing regimen and 40 mg EW dosing regimen, and these two dosing regimen produced comparable efficacy. No exposure-response relationship was observed in adult data.

(b) (4)

The key findings from the clinical pharmacology review are described in the sections below.

1.2.1 Induction Dosing Regimen

In patients with body weight ≥ 40 kg received 160 mg on Day 1 and 80 mg on Day 15 (160/80 mg) and patients with body weight < 40 kg received 80 mg on Day 1 and 40 mg on Day 15 (80/40 mg). There was no exposure-response relationship observed during the induction phase. Furthermore, trough concentrations and clinical remission at Week 4 were comparable with those in adults following 160/80 mg dosing regimen for both groups of patients. Thus, the proposed dosing regimens are acceptable.

1.2.2 Maintenance Dosing Regimen

The exposure-response relationship between trough concentrations at Week 26 and clinical remission based on unadjusted PCDAI at Week 26 showed that High Dose group achieved similar trough concentrations as those in adults and achieved greater clinical remission than the Low Dose group. This is consistent with results observed with dose response for clinical remission at week 26. There was trend in dose response showing that higher dose provided numerically higher benefit for other secondary endpoints (clinical remission at Week 52, clinical response at Week 26, and clinical response at Week 52). When clinical remission was evaluated over time, high dose consistently showed higher benefit than low dose during the maintenance.

Low Dose (20 mg EOW in patients with body weight ≥ 40 kg and 10 mg EOW in patients with body weight < 40 kg) produced lower levels of concentrations of adalimumab which led to lower rate of clinical remission at Week 26 and Week 52 when compared to High Dose. Furthermore, concentrations following low doses are lower than

concentrations observed with 40 mg EOW in adults. Trough concentrations and clinical remission at Week 26 following High Dose (40 mg EOW in patients with body weight ≥ 40 kg and 20 mg EOW in patients with body weight < 40 kg) were comparable with those in adults following 40 mg EOW dosing regimen. In addition, a higher proportion of patients in the low dose group got dose escalated due to a disease flare or inadequate response compared to the high dose group. Therefore, High Dose is recommended for the maintenance phase.

(b) (4)

1.2.4 Biopharmaceutics

The applicant proposed to market a new 10 mg/0.2 mL (50 mg/mL) prefilled syringe (PFS) presentation which has the identical formulation and container closure to the previously approved HUMIRA® PFS presentations but only differs in the fill volume. The proposed new PFS presentation is for administration of the 10 mg dose. Because the low dose is not recommended for the current sBLA, the registration of this new PFS presentation may not be needed.

Because the 20 mg/0.8 mL (25 mg/mL) vial was used in Study M06-806, the applicant requested an *in vivo* bioequivalence (BE) waiver for 10 mg/0.2 mL PFS.

The BE waiver request can be granted from a Clinical Pharmacology perspective as it is supported by the PK data obtained from Study DE029. Previously reviewed in the original BLA application, Study DE029 was a randomized, parallel-group, open-label study to assess BE between the currently marketed 50 mg/mL formulation and another 25 mg/mL formulation that was used in RA Phase 3 trials. Based on results from Study DE029, the two adalimumab formulations (50 mg/mL *vs.* 25 mg/mL) had comparable PK and the results met the conventional BE criteria for both C_{max} and $AUC_{0\text{-}360hr}$. These results indicated that the differences in adalimumab concentrations (50 mg/mL *vs.* 25 mg/mL) in product formulations did not have significant impact on adalimumab PK parameters including C_{max} and $AUC_{0\text{-}360hr}$.

1.2.5 Pharmacokinetics

In pediatric subjects with CD weighing ≥ 40 kg, the mean serum adalimumab concentration was 15.7 mcg/mL at Week 4, following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2. Following subcutaneous doses of 40 mg and 20 mg every other week, respectively, the mean steady-state trough serum adalimumab concentrations were 11.1 mcg/mL and 3.9 mcg/mL at Week 26 and 10.5 mcg/mL and 3.8 mcg/mL at Week 52.

In pediatric subjects with CD weighing < 40 kg, the mean serum adalimumab concentration was 10.6 mcg/mL at Week 4, following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2. Following subcutaneous doses of 20 mg and 10 mg every other week, respectively, the mean steady-state trough serum adalimumab concentrations were 8.3 mcg/mL and 2.7 mcg/mL at Week 26 and 6.9 mcg/mL and 2.6 mcg/mL at Week 52.

1.2.6 Immunogenicity

In Study M06-806, 182 subjects had the immunogenicity samples collected according planned schedule in the protocol. Of these 182 subjects, 58 subjects had at least one sample tested for ADA. A total of 6 subjects among the 58 subjects with samples tested were determined as ADA positive; therefore, the incidence of ADA development was 10.3% (6/58). The applicant also provided an alternate calculation of ADA formation rate based on the 182 subjects who received adalimumab treatment, which reported the ADA development rate of 3.3% (6/182). The remaining 124 subjects were not tested for ADA because all their immunogenicity samples had adalimumab concentration ≥ 2 mcg/mL which prevents the detection of ADA. Due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL.

The PK results indicated that ADA formation was associated with decreased adalimumab exposure in pediatric subjects with CD. The majority of PK samples in ADA positive subjects had serum adalimumab concentrations declined to below the lower limit of quantitation (LLOQ, 31.25 ng/mL) of the PK assay. The number of subjects who had ADA samples tested and confirmed to have developed ADA was too small to determine the effect of ADA on the efficacy or safety of adalimumab in pediatric subjects with CD.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is the relevant background information and regulatory history?

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human TNFα. Adalimumab consists of 1,330 amino acids and has a molecular weight of approximately 148 kDa.

HUMIRA® was initially approved for the treatment of RA (Rheumatoid Arthritis) in December 2002 and has been subsequently approved for other indications including psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, CD, ulcerative colitis, and plaque psoriasis. Following the approval for the adult CD indication in February 2007 (sBLA 125057/089), the applicant conducted studies in pediatric CD subjects 6 years of age and older to fulfill a post-marketing commitment (PMC#1). The Agency waived the pediatric study requirement for ages 0 to less than 6 years.

2.1.2 What are the proposed indications?

The proposed indications are for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who (b) (4) (b) (4) (b) (4)

2.1.3 What are the proposed dosing regimens?

Adalimumab is administered by subcutaneous (SC) injection. The proposed adalimumab dosing regimens are based on body weight and disease severity as shown in Table 1.

Table 1. Proposed Adalimumab Dosing Regiments for Pediatric Patients with CD

Patients	Induction Dose	Maintenance Dose (Starting at Week 4) (b) (4) (b) (4)
17 kg (37 lbs) to < 40 kg (88 lbs)	80 mg at Week 0, 40 mg at Week 2 (80/40 induction regimen)	20 mg EOW
≥ 40 kg (88 lbs)	160 mg at Week 0.80 mg at Week 2 (160/80 induction regimen)	40 mg EOW

The proposed dosing regimen also includes statements that some pediatric patients (b) (4) (b) (4) (b) (4) *Humira has not been studied in pediatric patients with CD aged less than 6 years.*

(b) (4)

2.2 What are the design features of the clinical studies to support the clinical pharmacology findings?

The proposed indication is supported by one pivotal trial (Study M06-806) and an ongoing extension trial (Study M06-807). Study M06-806 is a multicenter, randomized, double-blind clinical study to assess the efficacy, safety and pharmacokinetics (PK) of adalimumab in pediatric patients (aged 6-17 years) with moderate and severe active CD who had an inadequate response to conventional therapy including infliximab. Study M06-807 (interim analysis results) evaluated the long-term safety and tolerability of adalimumab in subjects who have demonstrated a clinical response in Study M06-806. This Clinical Pharmacology review is based on clinical study results of Study M06-806. Also, PK and efficacy information from the adult CD trials was utilized to support some of our recommendations.

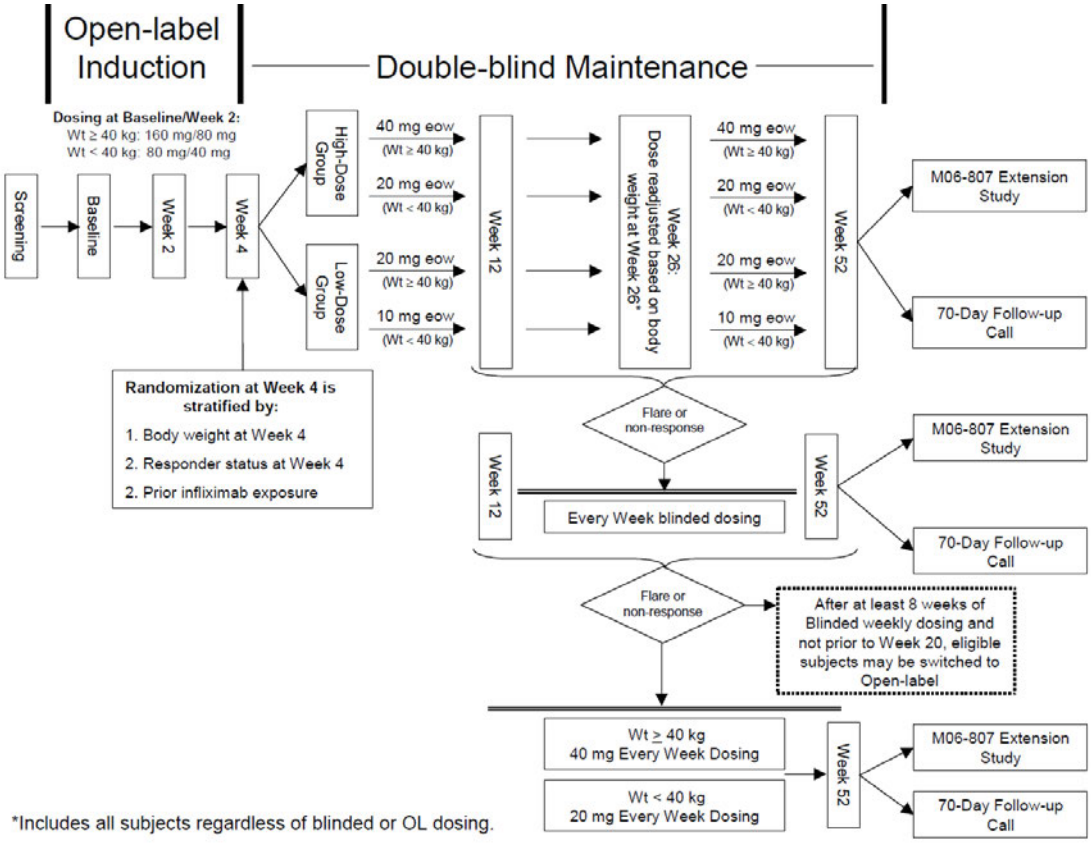

Figure 1. Schematic of study design (Source: *Figure 1, page 117, Adalimumab M06-806 Clinical Study Report, R&D/10/605)*

A total of 192 pediatric patients with moderate to severe CD were enrolled into Study. The study planned to include at least 80 subjects with age ≥ 13 years of age at Week 0 visit. One-third to one-half of the study population was to be subjects who have previously lost response to, or had intolerance to infliximab. The randomization was

stratified by the subjects' body weight at Week 4, responder status at Week 4, and prior infliximab use.

A summary of the Clinical Pharmacology study design features for Study M06-806 is as follows.

Dosing regimen

In Study M06-806, 192 pediatric subjects with moderately to severely active CD received open-label induction therapy at a dose based on their baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects weighing ≥ 40 kg (88 lbs) or 80 mg at Week 0 and 40 mg at Week 2 for subjects weighing < 40 kg. At Week 4, 188 subjects were randomized 1:1 to one of two maintenance dose regimens (High Dose vs Low Dose) based on body weight:

- High Dose: 20 mg for subjects weighing < 40 kg and 40 mg for subjects weighing ≥ 40 kg
- Low Dose: 10 mg for subjects weighing < 40 kg and 20 mg for subjects weighing ≥ 40 kg

At Week 12, subjects who experienced a disease flare (increase in the PCDAI of ≥ 15 points when compared to the Week 4 value and an absolute PCDAI above 30) or who were non-responders (did not achieve a decrease in the PCDAI of at least 15 points when compared to the baseline value for 2 consecutive visits at least 2 weeks apart) were allowed to switch from blinded every other week dosing to blinded every week dosing. Following an 8 week course of blinded EW treatment, subjects who continued to experience a disease flare or met the definition of non-response were allowed to switch to open-label every week therapy at Week 20. The dose of the open-label every week therapy was 20 mg for patients weighing < 40 kg and 40 mg for patients weighing ≥ 40 kg.

Efficacy measurements

The primary efficacy endpoint was rate of clinical remission (defined as PCDAI ≤ 10) at Week 26. Because Study M06-806 did not include placebo control group, the measure of trial success was to be the comparability of efficacy based on an external comparison with data from adults following 40 mg EOW dosing regimen (Study M06-404). The primary efficacy endpoint was modified to assess the success of the trial by comparing PCDAI clinical remission at Week 26 to CDAI clinical remission at Week 24 in an adult trial (Study M06-404). For the external comparison, correlations between CDAI scores and PCDAI scores in patients ≥13 years of age were evaluated to obtain conversion factors for patients ≥ 13 years of age and < 13 years for adjustment of PCDIA. The adjusted PCDAI clinical remission at Week 26 was then compared to CDAI clinical remission in adults at Week 24.

The secondary efficacy objects were to demonstrate the efficacy of adalimumab and to compare the two treatment groups with respect to 8 ranked secondary endpoints:

- Proportion of subjects in PCDAI clinical remission at Week 52

- Proportion of subjects in PCDAI clinical response at Week 26
- Proportion of subjects in PCDAI clinical response at Week 52
- Proportion of subjects in PCDAI clinical remission at Week 26 who were Week 4 responders
- PCDAI clinical remission at Week 4
- Proportion of subjects receiving corticosteroids at Baseline who had discontinued corticosteroids for at least 90 consecutive days prior to Week 26 and were in PCDAI clinical remission at Week 26
- Change from Baseline in z-score for height velocity at Week 26
- Change from Baseline in total IMPAC III scores at Week 26

PK measurements

Adalimumab serum concentrations were measured at baseline, Week 2, Week 4, Week 16, Wee 26 and Week 52 or early termination (ET).

Immunogenicity measurements

Serum anti-adalimumab antibodies (ADA) were measured at baseline, Week 16, Week 26 and Week 52 or ET.

2.3 Is there evidence of an exposure-response relationship in the maintenance phase for the proposed indication in pediatrics patients ≥ 6 years of age?

Yes, a statistically significant (p=0.006) exposure-response relationship between PCDAI clinical remission at Week 26 and observed trough concentration of adalimumab at Week 26 provides supportive evidence of effectiveness for adalimumab in the treatment of CD in pediatric patients (Figure 2).

Multivariate logistic regression analysis was conducted with PCDAI clinical remission at week 26 as the response variable. Several covariates were evaluated including sex, body weight, race, study, age, and baseline disease condition (Baseline PCDAI or Baseline CRP). Among these covariates, the adalimumab concentration was the only one significant predictor for clinical remission at Week 26.

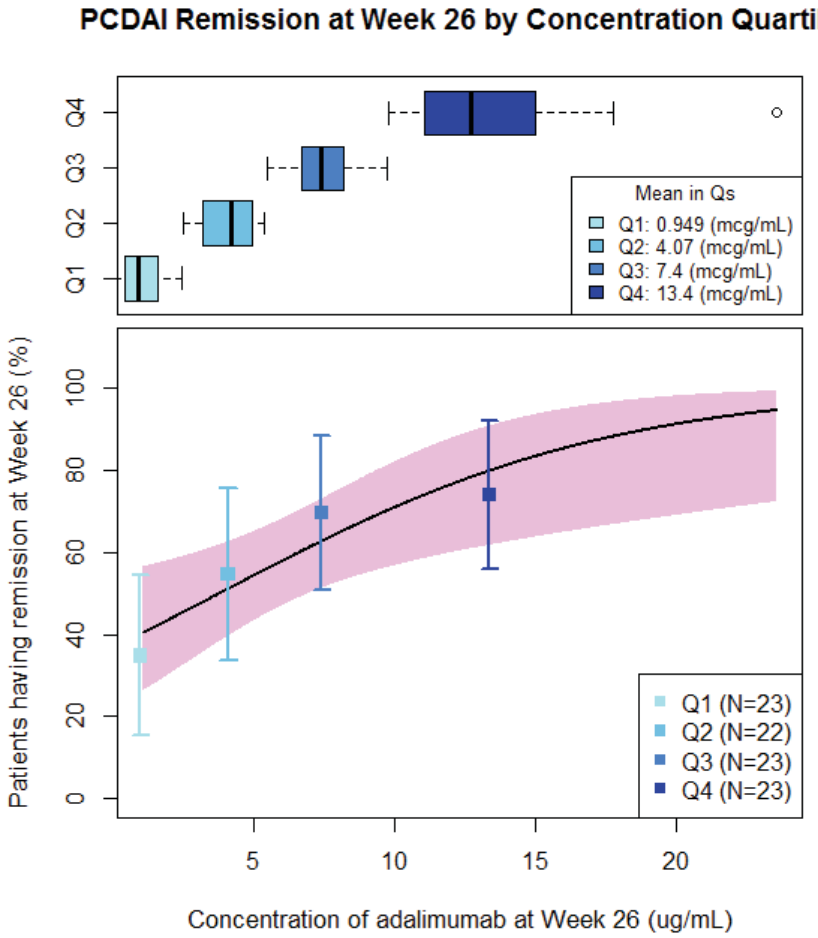

Figure 2. Logistic regression for PCDAI clinical remission at Week 26 by quartile of adalimumab trough concentration at Week 26 ***(Reviewer's analysis)***

Table 2. Summary of Mean Trough Concentration and PCDAI Clinical Remission at Week 26 by Quartile of Concentration of Adalimumab

	Subgroup	Ctrough (Mean ± SD)	Clinical Remission at Week 26
ER Dataset* **(N=91)**	Q1 (N=23)	0.95 ± 0.73	8/23 (34.8% [15.3, 54.2]
	Q2 (N=22)	4.07 ± 0.91	12/22 (54.5% [33.7, 75.4]
	Q3 (N=23)	7.4 ± 1.13	16/23 (69.6% [50.8, 88.4]
	Q4 (N=23)	13.4 ± 3.25	17/23 (73.9% [56.0, 91.9]

*(Reviewer's analysis: * Dataset includes patients whose concentrations at Week 26 are not missing and who did not get dose escalated until Week 26)*

2.4 Is the proposed dosing regimen for the induction phase appropriate?

Yes, the proposed dosing regimen of 160 mg on Day 1 and 80 mg on Day 14 (160/80 mg) for the ≥ 40 kg group and 80 mg on Day 1 followed by 40 mg on day 14 (80/40 mg) for BW < 40 kg appears reasonable.

The concentrations of adalimumab at Week 4 in patients with body weight < 40 kg following 80/40 mg dosing regimen were lower than those in patients with body weight ≥ 40 kg following 160/80 mg dosing regimen. However, there was no apparent exposure-response relationship between Week 4 adalimumab concentration and Week 4 clinical remission and clinical remissions at Week 4 are comparable between two groups of patients. Furthermore, concentrations of adalimumab at Week 4 appear to be comparable to those in adults. Concentrations of adalimumab at Week 4 in adults were 12.6 ± 5.25 mcg/mL (Study M02-403, N=67) and 12.6 ± 6.04 mcg/mL (Study M04-691, N=149), following 160/80 mg dosing regimen. As shown in Table 3, mean concentrations of adalimumab at Week 4 following 160/80 mg dosing regimen in patients with body weight ≥ 40 kg were 14.97 mcg/mL and those following 80/40 mg regimen in patients with body weight < 40 kg were 10.57 mcg/mL, which are comparable to those in adults following the approved dosing regimen 160/80 mg. Thus, the proposed dosing regimen with a body weight cut-off of 40 kg appears to be reasonable.

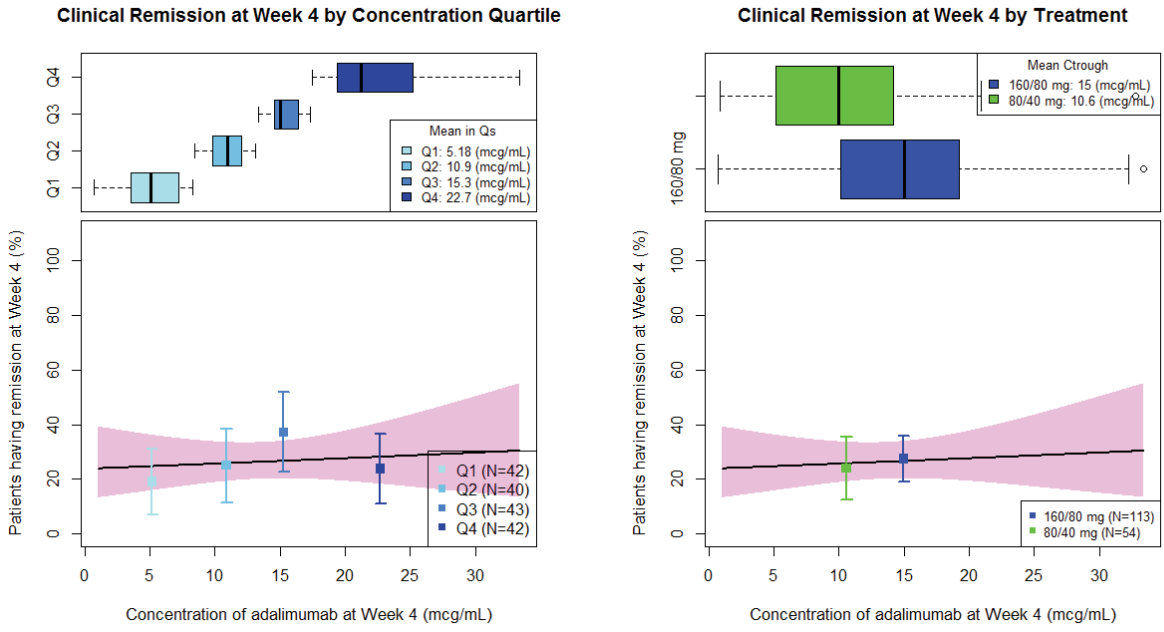

Figure 3. Exposure-response relationship between adalimumab concentration at Week 4 and clinical remission at Week4 ***(Reviewer's analysis)***

Table 3. Summary of Concentration of Adalimumab and Clinical Remission at Week 4 by Treatment Group and Population

Population	Subgroup	Dose	Ctrough (mcg/mL, Mean ± SD)	Clinical Remission at Week 4
Pediatrics	**< 40 kg (N=54)**	80/40 mg	10.57 ± 6.00	13/54 (24.1% [12.7, 35.5])
	≥ 40 kg (N=113)	160/80 mg	14.97 ± 6.94	31/113 (27.4% [19.2, 35.7])
Adults (M02-403)	**N=76**	160/80 mg	12.61 ± 5.25	27/76 (35.5%)
Adults (M04-691)	**N=159**	160/80 mg	12.63 ± 6.04	34/159 (21.4%)

(Reviewer's analysis for pediatrics. Source for adult data: M02-403 CSR Table 20, M02-403 PK Report page 4, M02-691 Table 16, M02-691 PK Report page 5)

2.4.1 Which dose is appropriate for maintenance phase?

High dose for the maintenance phase (40 mg EOW for ≥ 40 kg and 20 mg EOW for <40 kg pediatrics) recommended for both body weight groups based on the following observations:

- High Dose showed numerically higher efficacy for the primary endpoint and other top-ranked secondary endpoints (Table 4 and Table 5).
- Concentrations of adalimumab following Low Dose (10 mg in patients < 40 kg and 20 mg in patients weighing ≥ 40 kg) were less than the observed concentrations in adults following 40 mg EOW (Figure 4).
- High Dose consistently showed higher efficacy than low dose for clinical remission over time (Figure 5).
- More number of patients got dose escalated due to inadequate response in the Low Dose group compared to the High Dose group (Table 10).
- Dose-related toxicity within the dose range tested in the trial is unlikely of concern.

The adalimumab concentration and the clinical remission at Week 26 for each quartile are summarized in Table 2, and those for each treatment group are summarized in Table 4. The highest quartile (Q4) appears to be close to plateau in the exposure-response curve, and patients whose trough concentrations < 5 mcg/mL showed lower clinical remission. Considering that mean (±SD) trough concentration in adults (Study M06-433 in CD patients) following 40 mg EOW dosing regimen was 6.81 (±4.32) mcg/mL at Week 24 and 7.61 (±4.97) mcg/mL at Week 52, targeting exposure to Q3 (7.4 mcg/mL) in pediatric population is more appropriate. It should be noted that the mean concentrations of adalimumab following low doses (10 mg for patients with body weight < 40 kg and 20 mg for patients with body weight ≥ 40 kg) fall into the regions that are

less than the third quartile (Q3) and their corresponding remission rates are lower than those in patients who received high doses.

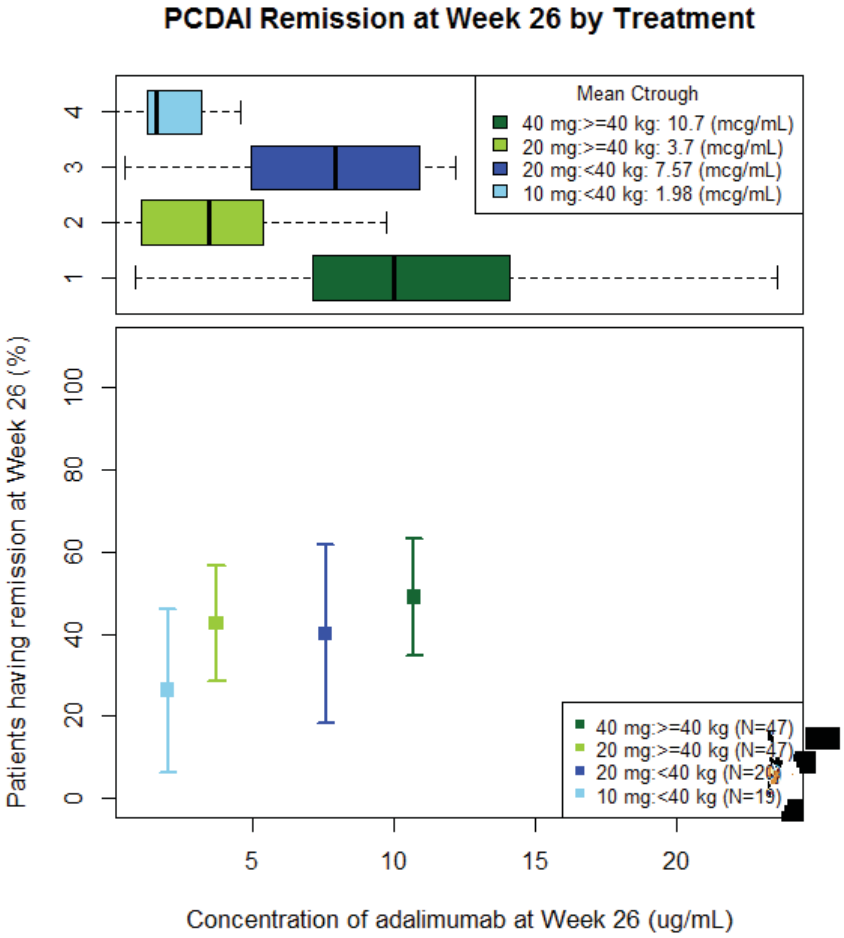

Figure 4. PCDAI clinical remission at Week 26 (N=133, subjects who stayed with the original therapy until Week 26) ***(Reviewer's analysis)***

Table 4. Summary of Mean Trough Concentration and PCDAI Clinical Remission at Week 26 by Treatment Group

		Dose	Ctrough (Mean ± SD)	Clinical Remission at Week 26
	N		91 (42 missing)	133
ER dataset II (N=133; subjects who stayed with the original therapy until Week 26)	**< 40 kg (N=39)**	10 mg (N=19)	1.98 ± 1.41	5/19 (26.3% [6.5, 46.1])
		20 mg (N=20)	7.57 ± 3.62	8/20 (40.0% [18.5, 61.5])
	≥ 40 kg (N=94)	20 mg (N=47)	3.7 ± 2.71	20/47 (42.6% [28.4, 56.7])
		40 mg (N=47)	10.7 ± 4.6	23/47 (48.9% [34.6, 63.2])

(Reviewer's analysis)

Table 5. Secondary Efficacy Endpoints by Body Weight and Dose Group

Body Weight	Dose	Clinical Response at Week 26	Clinical Remission at Week 52	Clinical Response at Week 52
< 40 kg (N=60)	**10 mg (N=31)**	13/31 (41.9%)	5/31 (16.1%)	8/31 (25.8%)
	20 mg (N=29)	14/29 (48.3%)	8/29 (27.6%)	11/29 (37.9%)
≥ 40 kg (N=128)	**20 mg (N=64)**	33/64 (51.6%)	17/64 (26.6%)	19/64 (29.7%)
	40 mg (N=64)	41/64 (64.1%)	23/64 (35.9%)	28/64 (43.8%)

(Reviewer's analysis)

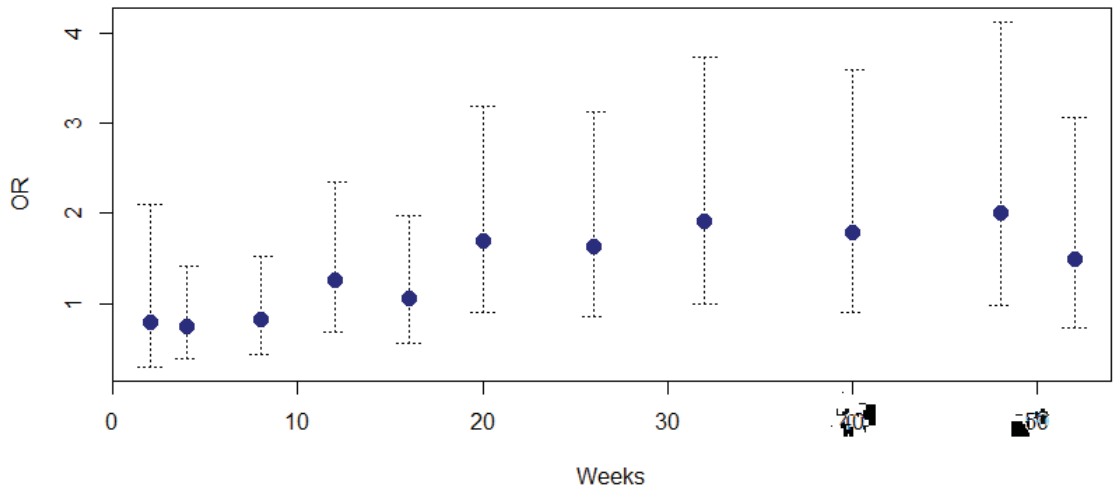

Figure 5. Odds ratio for High Dose relative to Low Dose for Clinical Remission over time ***(Reviewer's analysis)***

Nonetheless, clinical remission at Week 26 in these patients (Low Dose (10/20 mg): 28.4%) was lower than that in patients receiving higher dosing regimens (High Dose (20/40 mg): 38.7%).

As shown in Figure 6, the majority of patients in the lower quartiles (Q1 and Q2) appear to have received low doses (top left panel), implying low doses produce lower concentrations than those in adults.

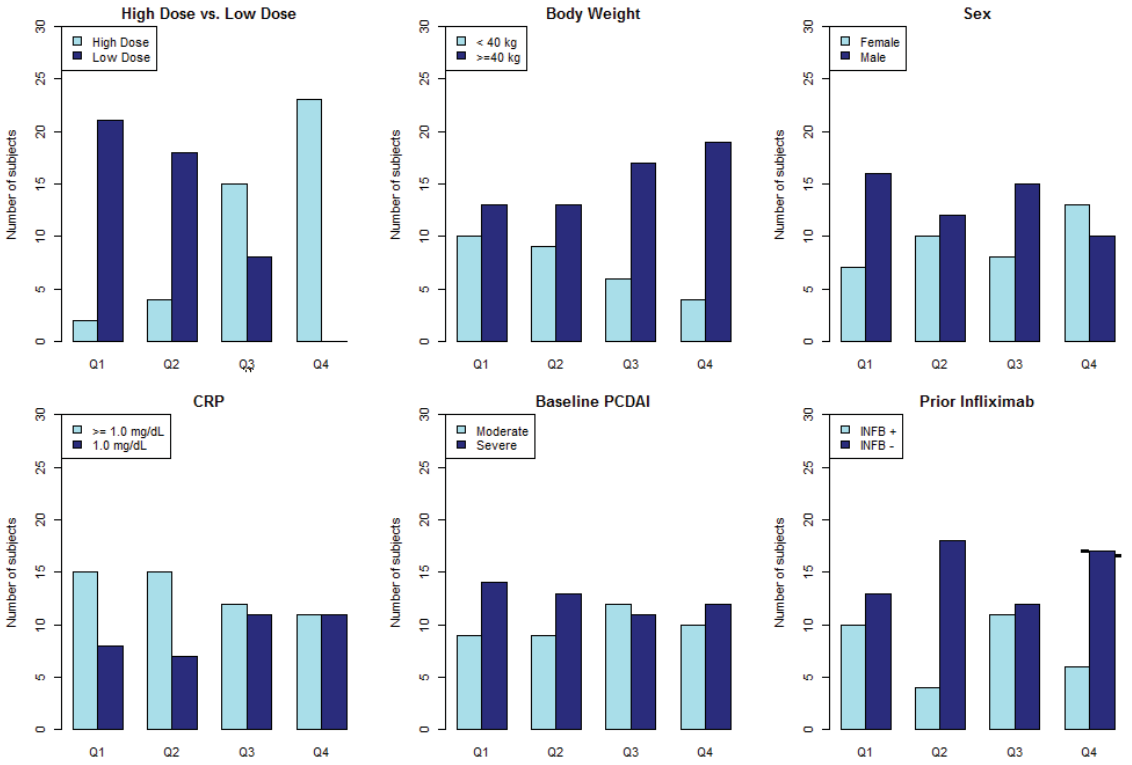

Figure 6. Baseline risk factors in quartile of trough concentration of adalimumab at Week 26 (N=91) ***(Reviewer's analysis)***

Table 6. Risk factors in each quartile of exposure (N=91)

	Low Dose	**Body Weight < 40 kg**	**Female**	**Baseline CRP ≥ 1.0 mg/dL***	**Baseline PCDAI ≥ 40***	**Prior INFB Use**
Q1 (N=23)	21 (91%)	10 (44%)	7 (30%)	15 (65%)	14 (61%)	10 (43%)
Q2 (N=22)	18 (82%)	9 (41%)	10 (45%)	15 (68%)	13 (59%)	4 (18%)
Q3 (N=23)	8 (35%)	6 (35%)	8 (35%)	12 (52%)	11 (48%)	11 (48%)
Q4 (N=23)	0	4 (21%)	13 (57%)	11 (50%)	12 (55%)	6 (26%)

*(Reviewer's analysis: *data for one patient missing)*

It should be also noted that the majority of patients with body weight ≥ 40 kg who received 20 mg EOW also fell into the lower quartiles (Figure 7), suggesting not only 10 mg in patients with body weight < 40 kg but also 20 mg with body weight ≥ 40 kg may not be the optimal dose to aim comparable efficacy in adults. Other baseline risks such as CRP (C-reactive protein) or Baseline PCDAI seem to be associated with the exposure but not as significant as dose

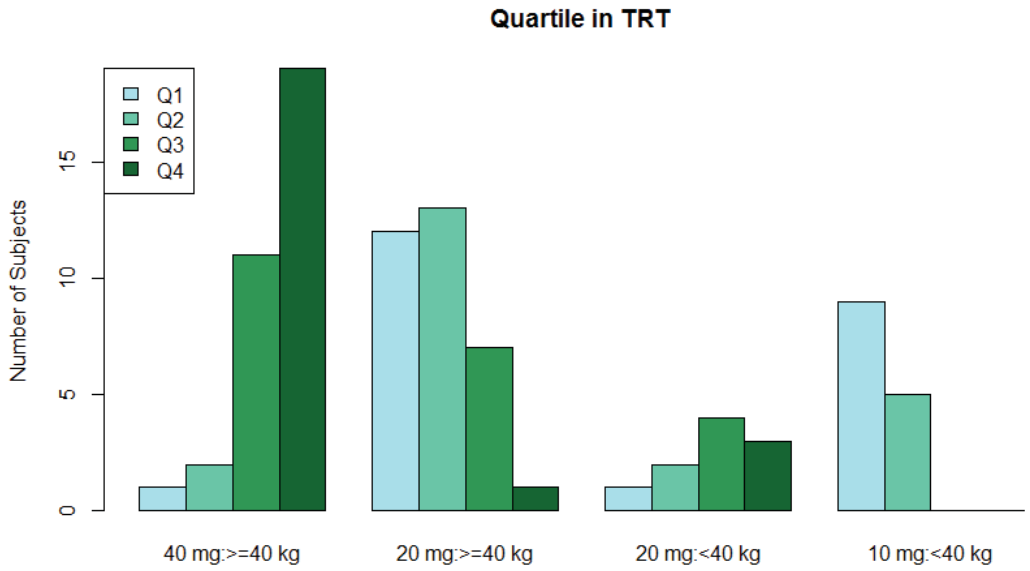

Figure 7. Distribution of quartile of trough concentration at Week 26 by body weight and dose groups ***(Reviewer's analysis)***

The adverse events are summarized by treatment group in Table 7. Safety profiles appear to be similar between high dose and low dose for patients with body weight ≥ 40 kg but rates of adverse events appear to be higher in high dose (20 mg) in patients with body weight < 40 kg. According the clinical reviewer's review, most of the high rates in this group of patients seemed to be associated with disease conditions (refer to Dr. Marjorie Dannis' clinical review for details). Thus, dose-related toxicity within the dose range tested in the trial is unlikely of concern. Among the patients who stayed with EOW dosing regimen until Week 26, the mean trough concentrations of adalimumab at Week 26 in the patients with body weight < 40 kg receiving 10 mg EOW dosing regimen and in patients with body weight ≥ 40 kg receiving 20 mg EOW dosing regimen were less than 6.81 mcg/mL which was the mean concentration observed in adults at Week 24.

Table 7. Summary of Adverse Events by Body Weight and Dose Group

	BW < 40 kg		**BW ≥ 40 kg**	
	10 mg (N=31)	**20 mg (N=29)**	**20 mg (N=64)**	**40 mg (N=64)**
Any AE	24 (77.4)	26 (89.7)	57 (89.1)	60 (93.8)
At least possibly TE	11 (35.5)	9 (31.0)	35 (40.6)	30 (46.9)
Severe AE	4 (12.9)	**9 (31.0)**	7 (10.9)	10 (15.6)
Serious AE	4 (12.9)	**10 (34.5)**	15 (23.4)	12 (18.8)
Leading to DC	3 (9.7)	**8 (27.6)**	9 (14.1)	7 (10.9)

At least possibly TE-SAE	0	0	2 (3.1)	1 (1.6)
Infections AE	14 (45.2)	19 (65.5)	33 (51.6)	37 (57.8)
Serious infections	1 (3.2)	2 (6.9)	2 (3.1)	3 (4.7)

(Source: Clinical Study Report M06-806 Table 75, page 353)

(b) (4)

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2.7 Biopharmaceutics

2.7.1 What are the adalimumab formulations used in Studies M06-806 and M06-807 and what are the reasons for the in vivo bioequivalence waiver request?

The adalimumab formulations used in Studies M06-806 and M06-807 are summarized in Table 12. The applicant requested an *in vivo* BE waiver because the applicant proposed to market 10 mg/0.2 mL PFS for HUMIRA® instead of 20 mg/0.8 mL vial that was used in the pediatric trials.

Table 12. Dosage Form and Strengths Used in Studies M06-806 and M06-807

Pediatric subjects with CD	**(doses used in the trial): dosage form and strength**		
	Induction (Week 0, 2)	Maintenance (Week 4-52)	Long-term (Week 52-264)
body weight < 40 kg	(80 mg → 40 mg):	(20 mg): 40 mg/ 0.8 mL vial	20 mg/0.4 mL PFS

	40 mg/0.8 mL vial	(10 mg): 20 mg/0.8 mL vial	
body weight ≥ 40 kg	(160 mg → 80 mg): 40 mg/0.8 mL vial	(40 mg): 40 mg/ 0.8 mL vial	40 mg/0.8 mL PFS
		(20 mg): 20 mg/ 0.8 mL vial	

(PFS, pre-filled syringe)

The proposed 10 mg/0.2 mL PFS has the identical formulation and container closure to the previously approved HUMIRA® PFS presentations but only differs in the fill volume. HUMIRA® is currently marketed as vial (40 mg/0.8 mL), PFS (40 mg/0.8 mL and 20 mg/0.4 mL), and Pen (40 mg/0.8mL), all using the same formulation with adalimumab strength of 50 mg/mL.

2.7.2 Are there sufficient PK data to support the BE waiver request for 10 mg/0.2 mL PFS?

Yes, the BE waiver request is supported by the PK comparability data in Study DE029 where PK results showed that the differences in adalimumab concentrations (50 mg/mL *vs.* 25 mg/mL) in the product formulation did not have significant impact on adalimumab PK parameters including C_{max} and $AUC_{0\text{-}360hr}$.

However, the proposed new PFS presentation (10 mg/0.2 mL) is for administration of the 10 mg dose. Because the low dose is not recommended for the current sBLA, the registration of this new PFS presentation may not be needed.

Previously reviewed in the original BLA application, Study DE029 was a randomized, parallel-group, open-label study to assessed the BE between the currently marketed 50 mg/mL formulation and another 25 mg/mL formulation that was used in RA Phase 3 trials. Compared to the 25 mg/mL formulation used in Study M06-806, the 25 mg/mL formulation used in the RA trials had similar formulation composition with the exception of not containing Tween 80. The PK data from Study DE029 showed that the two adalimumab formulations (50 mg/mL *vs.* 25 mg/mL) had comparable PK and the results met the conventional BE criteria for both C_{max} and $AUC_{0\text{-}360hr}$. The BE analysis results are summarized in Table 13. Refer to the Clinical Pharmacology review of the original BLA application for more details.

Table 13. BE Assessment on the 50 mg/mL Formulation *vs.* 25 mg/mL Formulation in Study DE029

PK parameters	Estimate of population Central value		Relative bioavailability	
	25 mg/mL (*Test*)	50 mg/mL (Reference)	Point estimate	90% confidence interval
Cmax	4.478	4.741	0.944	0.857-1.041
$AUC_{0\text{-}360}$	1173.0	1263.2	0.929	0.850-1.014

(*Data source: Table 9, page 12, summary of biopharmaceutics studies and analytical methods*)

2.8 Pharmacokinetics

2.8.1 What were the PK characteristics of adalimumab in pediatric subjects with CD? How was the adalimumab exposure compared to that observed in adult subjects with CD?

Induction treatment

In pediatric subjects weighing ≥ 40 kg receiving subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2, the mean (±SD) serum adalimumab trough concentration at Week 4 was 15.7±6.6 mcg/mL (n=123). In pediatric subjects weighing < 40 kg receiving subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2, the mean (±SD) serum adalimumab trough concentration at Week 4 was 10.6±6.1 mcg/mL (n=69) (*Data source: Table 3, summary of Clinical Pharmacology studies*). In adult patients with CD receiving subcutaneous dose of 160 mg HUMIRA at Week 0 and 80 mg at Week 2, the mean serum adalimumab trough levels were approximately 12 mcg/mL Week 4 (*Data source: HUMIRA USPI*).

Maintenance treatment

In pediatric subjects weighing ≥ 40 kg who remained on their original randomized therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 10.5±6.0 mcg/mL and 3.8±2.2 mcg/mL, respectively, for 40 mg and 20 mg doses administered subcutaneously every other week. In pediatric subjects weighing < 40 kg, the mean (±SD) adalimumab trough concentrations at Week 52 were 6.9±3.6 mcg/mL and 2.6±2.0 mcg/mL, respectively, for 20 mg and 10 mg doses administered subcutaneously every other week (Table 14). In adult patients with CD, the mean steady-state trough level was approximately 7 µg/mL at Week 24 and Week 56 after receiving a maintenance dose of 40 mg HUMIRA every other week.

Reviewer's comment: *The PK results indicated that the pediatric subjects receiving low doses of HUMIRA (20 mg EOW for ≥40 kg and 10 mg EOW for <40 kg) had generally lower steady state exposure than that observed in adult subjects receiving approved doses of 40 mg EOW.*

Table 14. Summary of Serum adalimumab Trough Concentrations in Pediatric Subject with CD Who Remained on Their Original Randomized Therapy

Treatment groups	Dose (body weight, n)	Adalimumab concentrations (Mean ± SD, mcg/mL)				
		Week 2	Week 4	Week 16	Week 26	Week 52
High Dose (40/20 mg EOW)	Combined (N=53)	16.2±6.07	15.5±6.74	10.3±4.80	10.4±4.26	9.48±5.61
	40 mg EOW (≥ 40 kg, N=36)	16.4±5.61	16.2±6.54	11.3±4.82	11.1±4.50	10.5±5.99

	20 mg EOW (< 40 kg, N=17)	15.7±7.09	14.1±7.13	7.73±3.83	8.32±2.62	6.89±3.55
Low Dose (20/10 mg, EOW)	Combined (n=45)	14.6±4.77	12.4±6.17	3.98±2.38	3.63±2.50	3.51±2.21
	20 mg EOW (≥ 40 kg, N=34)	15.1±4.89	12.8±6.47	4.25±2.52	3.90±2.69	3.80±2.24
	10 mg EOW (< 40 kg, N=11)	13.1±4.22	11.2±5.27	3.07±1.63	2.70±1.48	2.60±2.00
Adult data as reference*		**Week 4**	**Week 4**		**Week 24**	**Week 56**
	160 mg/80 mg at Weeks 0/2	12.34 ± 3.68	12.61 ± 5.25	NA	NA	NA
	40 mg EOW	NA	NA	NA	8.20 ± 4.69	10.92 ± 6.57

(Data source: Table 4 and Table 5, Adalimumab M06-806 Pharmacokinetic Report R&D/10/97; M02-403 for induction phase and M02-433 for maintenance phase)

2.9 Immunogenicity

2.9.1 What is the incidence of ADA formation in pediatric subjects with CD?

In Study M06-806, 182 subjects had the immunogenicity samples collected according planned schedule in the protocol. Immunogenicity samples were collected at the baseline, Week 16, Week 26 and Week 52 or early termination (ET) visits. Of these 182 subjects, 58 subjects had at least one sample tested for ADA. The remaining 124 subjects were not tested for ADA because all their immunogenicity samples had adalimumab concentration ≥ 2 mcg/mL. Due to the limitation of the assay conditions, ADA to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL.

A total of 6 subjects were determined as ADA positive. Of the 58 subjects who had at least one sample tested for ADA, the rate of ADA development was 10.3% (6/58). Of the 182 subjects who received adalimumab treatment, the rate of ADA development was 3.3% (6/182).

2.9.2 What are the impacts of immunogenicity on adalimumab PK, efficacy and safety?

The efficacy (remission at Week 26) and serum adalimumab concentrations for the 6 ADA+ subjects are summarized in Table 15.

Table 15. List of ADA Positive Subjects in Study M06-806 and Their Individual Efficacy and PK Results

Treatment group	Subject ID	Week became ADA+	Remission at Week 26	PK results: adalimumab concentrations (mcg/mL) at Weeks of					
				2	4	16	26	52	ET
Low dose (20/10 mg EOW)	(b) (6)	ET	No	16.7	0.735	N/A	N/A	N/A	0
		16	Yes	10.3	0.868	0	0	0	N/A
		16	No	14.7	5.68	0	N/A	N/A	0
		52	Yes	13.6	5.02	0	0	0	N/A
High dose (40/20 mg EOW)		16	No	7.24	9.36	0	2.92#	9.24	N/A
		16	No	16.8	3.5	0	0	0	N/A

*Subjects (b) (6) (last dose on Week 8) and (b) (6) (last dose on Week 22) terminated the study early before Week 26 due to withdrawn consent and lack of efficacy, respectively. #Subject (b) (6) received high dose 40 mg EOW dosing regimen and had dose escalation to weekly dosing starting from Week 26. ET, early termination; N/A, data not available; adalimumab concentrations <LLOQ is presented as 0 mcg/mL; (*Data source: Table 15, Page 73, Adalimumab M06-806 Pharmacokinetic Report R&D/10/977*)

The PK results indicated that ADA formation was associated with decreased adalimumab exposure in pediatric subjects with CD. The majority of PK samples in ADA positive subjects had serum adalimumab concentrations declined to below the lower limit of quantitation (LLOQ, 31.25 ng/mL) of the PK assay.

The number of subjects who had ADA samples tested and confirmed to have developed ADA was too small to determine the effect of ADA on the efficacy or safety of adalimumab in pediatric subjects with CD. Among the 6 ADA positive subjects, 2 subjects ((b) (6) and (b) (6)) achieved remission at Week 26. Regarding safety, no serious infections, malignancy, or death was observed in pediatric subjects who developed ADA in Study M06-806.

2.10 Bioanalytical methods

2.10.1 What bioanalytical methods were used to determine adalimumab concentrations in serum? Briefly describe the performance of the assay.

Adalimumab concentrations in serum were determined using a validated enzyme-linked immunoadsorbent assay (ELISA). The original assay validation was submitted and reviewed in the original RA application. The ELISA assay was revalidated and used for measurement of PK samples in Study M06-806. The performance of the revalidated assay is summarized in Table 16.

Table 16. Summary of Assay Revalidation Results of the ELISA for Measurement of Serum Adalimumab Concentration

Assay Parameters	Assay conditions		Validation results		
Precision and accuracy			Accuracy (%)	Between run precision (%CV)	Within run precision (%CV)
	QC concentrations	LLOQ (31.25 ng/mL)	13.4	4.8	3.2
		Low (40.0 ng/mL)	4.0	5.6	3.7
		Medium (250 ng/mL)	-1.4	2.3	3.7
		High (380 ng/mL)	2.9	2.9	5.4
		ULOQ (500 ng/mL)	13.1	6.4	3.9
	QC dilution (4000 ng/mL)	1:1000	3.6	10.4	2.6
		1:100	3.2	5.7	3.3
Selectivity and specificity	Background determination in 10 individual human serum samples		All 10 samples <31.25 ng/mL (LLOQ)		
	Spike recovery with 40.0 ng/mL in the same 10 individual human serum samples		All 10 results were within 75-125%		
	Spike recovery with 380 ng/mL in the same 10 individual human serum samples		All 10 results were within 80-120%		
Assay range	Diluted		3.125-50 ng/mL		
	Undiluted		31.25-500 ng/mL		

(*Data source: Table 1 and 2, summary of biopharmaceutics studies and analytical methods*)

2.10.2 What bioanalytical methods and strategies were used for ADA assessment?

Serum ADA was assayed by an ELISA based on a double-antigen technique developed and used since the original BLA application. The assay detects free (unbound) ADA. Due to the historical drug interference issue of the ELISA assay, ADA could be detected only when serum adalimumab levels were <2 mcg/mL. In the characterization of immunogenicity sample ADA status, the sponsor first measured the adalimumab concentration in the sample, and ADA assessment was conducted only on samples with serum adalimumab concentrations less than 2 mcg/mL whereas serum samples with adalimumab concentrations ≥2 mcg/mL were not analyzed for ADA. Because of the limitations of the assay, two different ways of calculating the incidence rate of ADA formation were used in the current sBLA application, which is reasonable (*see section 2.5.1*).

The applicant is currently developing an improved immunogenicity assay to fulfill PMR #3 listed in the FDA approval letter of BLA 125057/232 (UC indication) dated September 28, 2012. Therefore, there are no further recommendations to the sponsor to improve the drug tolerance level of the immunogenicity assay based on this Clinical Pharmacology review.

3 LABELING

Detailed labeling revisions are summarized as below. The sections in red are the labeling changes proposed by the Applicant. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer. The texts in blue are recommended labeling changes by the reviewer. The *italic texts* provide the labeling recommendations rational based on this clinical pharmacology review.

Proposed labeling by the applicant and labeling recommendations by this reviewer	Labeling recommendation rationale
-------**DOSAGE AND ADMINISTRATION**------- **Pediatric Crohn's Disease (2.4)** ***17 kg (37 lbs) to < 40 kg (88 lbs):*** Initial dose (Day 1) is 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose (b) (4) of 20 mg every other week. (b) (4) ***≥ 40 kg (88 lbs):*** 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 40 mg injections in one day) two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose (b) (4) (b) (4) of 40 mg every other week. (b) (4) (b) (4)	
6 ADVERSE REACTIONS **6.1 Clinical Trials Experience** Immunogenicity In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was (b) (4) %. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 µg/mL. Among the patients whose serum adalimumab levels were < 2 µg/mL (approximately 32% of total patients studied), the immunogenicity rate was (b) (4) %.	*The proposed labeling by the applicant is acceptable (see Section 2.5.1).*
12.3 Pharmacokinetics (b) (4)	*See Section 2.4. The recommended labeling changes are based on recommended dosing regimen.*

(b) (4)	
In pediatric subjects with CD weighing ≥ 40 kg, the mean±SD serum adalimumab concentrations were 15.7± (b) (4) mcg/mL at Week 4 following subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 and the mean steady-state trough serum adalimumab concentrations were 10.5±6.0 mcg/mL (b) (4) at Week 52 following subcutaneous doses of 40 mg (b) (4) every other week- (b) (4). In pediatric subjects with CD weighing < 40 kg, the mean±SD serum adalimumab concentrations were 10.6±6.1 mcg/mL at Week 4 following subcutaneous doses of 80 mg at Week 0 and 40 mg at Week 2 and the mean±SD steady-state trough serum adalimumab concentrations were 6.9±3.6 mcg/mL (b) (4) at Week 52 following subcutaneous doses of 20 mg (b) (4) every other week- (b) (4)	

4 REULTS OF SPONSOR'S ANALYSIS

4.1 Introduction

The analysis was based on non-responder imputation (NRI). Subjects who prematurely discontinued the study, or who switch from double-blind EOW to EW dosing, or who discontinue double-blind EOW treatment before the scheduled evaluation of clinical remission, or who do not have the relevant PCDAI score was considered to have not achieved clinical remission; failure was imputed for such subjects.

Due to the absence of a placebo group comparative data in the study, decision concerning the success or failure of the study was based on both internal and external efficacy comparison. The internal comparison of PCDAI clinical remission at Week 26 was made between the randomized treatment groups (high dose vs. low dose).

The sponsor claims the validity of PCDAI as a disease activity measure has been accepted by clinical community and the CDAI show good correlation with PCDAI (R=0.86). According to the clinical review for Remicade for pediatric Crohn's disease, the PCDAI measure appears to be more strict than CDAI measure (refer to the review of Dr. John Hyde date May 18, 2006).The sponsor claims that the PCDAI scores include more objective measures than CDAI score related to disease manifestations in children, such as changes in height and albumin levels (PCDAI score includes fewer contributions than the CDAI score from subjective measure, such as abdominal pain and general well-being, which are likely to be less consistently assessed by children than adults). According to the FDA review for infliximab (Remicade®) for pediatrics CD (refer to Dr. John Hyde's review dated May 18, 2006), the PCDAI appeared to be more stringent that remission criteria based on CDAI. The CDAI score ranges from 0 to 600 and the PCDAI score ranges from 0 to 100.

The Study M06-806 was initially designed to provide 80% power to detect difference between Low Dose and High Dose in pediatric patients older than 6 years of age,

assuming clinical remission of 40% in High Dose and 20% in Low Dose. The success measure of the study, however, was planned to be determined based on the 95% CI for the difference in remission rates at Week 26 between Study M06-806 and Study M0-404. Due to the difficulty in direct comparison of these two measurements, the sponsor estimated a conversion factor with CDAI data available patients ≥ 13 year of age and then applied to the whole population for external comparison with adult data (primary efficacy endpoint). In terms of proportion of patients who were previously experience with other anti-TNF agents in the two studies was similar.

The sponsor conducted a population PK analysis and exposure-response analysis for adalimumab in pediatrics with moderate to severe CD with data from Study M06-806. The objectives of the study was to characterize the population PK of adalimumab in pediatric patients with CD and the relationship between exposure and clinical remission as measured by PCDAI, following administration of two dosage regimens of adalimumab in the induction and maintenance of clinical remission in pediatric subjects with moderate to severe CD. Typical PK parameters were estimated from the population PK analysis, and those parameters were used to model the relationship between adalimumab exposure and remission. A continuous time Markov model approach was used for the exposure-response analysis. Simulations of various clinical scenarios were conducted based on the final model.

4.2 Datasets

For efficacy analysis, ITT analysis data set was used (N=188) which excludes 4 subjects who were not randomized at Week 4. Of all the subjects enrolled in Study M06-806 (N=192), three subjects ([(b) (6)], [(b) (6)], and [(b) (6)]) were excluded from the PKPD analysis. These subjects received only one dose of adalimumab and had none or only one measurable adalimumab serum concentration above the lower limit of quantitation (LLOQ). The data from the remaining randomized subjects (N=189) were included in the exposure-response analyses. Summary of key demographic data for the subjects included in the analysis dataset is presented in Table 17.

Table 17. Demographic Data Summary for PKPD Analyses

Demographic Characteristic		Adalimumab Treated (N = 189)
Sex, N (%)	Male	105 (55.6%)
	Female	84 (44.4%)
Race, N (%)	White	167 (88.4%)
	Other	22 (11.6%)
Age (years)	Mean ± SD (Range)	13.6 ± 2.49 (6 – 17)
Baseline Body Weight (kg)	Mean ± SD (Range)	45.3 ± 15.37 (19 – 120)

(Source: Population PK Exposure-Response Report Table 1)

4.3 Results

4.3.1 Efficacy

The primary external comparison of the **adjusted** PCDAI-based clinical remission rates of the High-Dose (46.8%) and overall adalimumab treatment (46.2%) showed that these rates exceeded the CDAI-based remission rate in the adult Study M02-404 (33.5%), and the Low-Dose adalimumab treatment (44.7%) had an **adjusted** clinical remission rate comparable to the clinical remission rate of the adult study.

Table 18. External Comparison of Proportion of Subjects in PCDAI Clinical Remission at Week 26 (ITT Analysis set, NRI, *adjusted by conversion factor*)

Adalimumab	N	Proportion of Subjects in Remission[a]	Difference[b]	95% CI[c]
Study M02-404 (40 mg eow [ITT])	260	33.46	--	--
Study M06-806 Low-Dose	95	44.66	11.20	–0.33, 22.73
Study M06-806 High-Dose	93	46.77	13.31	1.66, 24.96
Study M06-806 Overall	188	46.17	12.71	3.56, 21.86

(Source: Clinical Study Report for M06-806 Table 25, page 236)

The sponsor further conducted analysis for the PCDAI clinical remission at Week 26 by Week 4 body weight category (< 40 kg, ≥ 40 kg) without adjustment with conversion factor. As shown in Table 19, clinical remission rates at Week 26 are higher in High Dose group compared to Low Dose group for both body weight categories.

Table 19. Analysis of PCDAI Clinical Remission at Week 26 by Week 4 Weight Category (ITT Analysis, NRI, without adjustment by conversion factor)

Week 4 Weight Category	Adalimumab Low-Dose 20 mg or 10 mg eow n/N (%)	Adalimumab High-Dose 40 mg or 20 mg eow n/N (%)	Adalimumab Overall n/N (%)	Difference[a]	95% CI[b]	*P* value[c]
< 40 kg	6/31 (19.4)	10/29 (34.5)	16/60 (26.7)	15.13	–7.07, 37.32	0.103
≥ 40 kg	21/64 (32.8)	26/64 (40.6)	47/128 (36.7)	7.81	–8.83, 24.46	0.306

(Source: Clinical Study Report for M06-806 Table 29, page 246)

The results for secondary endpoints are summarized in the Table 20. The clinical remission and clinical response at Week 4, Week 26, and Week 52 appear to be consistently higher in High Dose group compared to Low Dose group.

Table 20. Summary of Results of Ranked Secondary Endpoints

Ranked Secondary Endpoint[a]	Number (%) of Subjects: Low-Dose[b] N = 95	Number (%) of Subjects: High-Dose[b] N = 93	*P* value[c]
1. PCDAI clinical remission at Week 52	22 (23.2)	31 (33.3)	0.100
2. PCDAI clinical response at Week 26	46 (48.4)	55 (59.1)	0.073
3. PCDAI clinical response at Week 52	27 (28.4)	39 (41.9)	0.038

	M06-806 N	M06-806 %	M02-404 mITT[d] Set N = 172 %	95% CI[e]
4. PCDAI clinical remission at Week 26 for subjects who were responders at Week 4[f]			39.53	
Overall	155	52.02		1.75, 23.22
High-Dose	75	54.00		1.03, 27.90
Low-Dose	80	49.34		–3.36, 22.98

	M06-806 N = 192	M02-404 Overall N = 854	
5. PCDAI clinical remission at Week 4[f]	55.63	25.29	22.73, 37.95

	Low-Dose[b] N = 38	High-Dose[b] N = 33	*P* value[c]
6. PCDAI clinical remission at Week 26 and discontinued corticosteroids for ≥ 90 days, for subjects using corticosteroids at Baseline	9 (23.7)	10 (30.3)	0.329

Ranked Secondary Endpoint[a]	Mean ± SD: Low-Dose[b] N = 61	Mean ± SD: High-Dose[b] N = 68	*P* value[g]
7. Change from Baseline in "z"-scores for height velocity at Week 26[h]	2.64 ± 4.142	1.75 ± 5.288	0.481

	Mean ± SD: Low-Dose[b] N = 90	Mean ± SD: High-Dose[b] N = 86	*P* value[g]
8. Change from Baseline in total IMPACT III scores at Week 26	17.20 ± 20.195	18.33 ± 19.691	0.847

(Source: Clinical Study Report for M06-806 Table 30, page 248)

Reviewer's comments: The primary efficacy endpoint was comparability between adjusted PCDAI-based clinical remission in pediatrics patients and CDAI-based clinical remission in adults. The validity of the conversion factor which was used in adjustment of PCDAI is questionable because the dose-response observed from unadjusted PCDAI disappeared by adjustment with the conversion factor. As seen in Table 18, the adjusted PCDAI does not show difference between Low Dose and High Dose but the difference

between these two dose groups for PCDAI is clearly observed from unadjusted PCDAI (Table 19).

4.3.2 Safety

Adverse events are summarized by treatment group in table. There appears no difference in adverse event rates across body weight group and dose group except for the serious adverse events.

Reviewer's comments: According to the clinical reviewer (refer to the clinical review by Dr. Marjorie Dannis), the higher rate for serious adverse events observed in 20 mg dose group < 40 kg (34.5%) appeared to be associated with Crohn's disease and not likely related to treatment.

Table 21. Proportion of Subjects with TEAEs by Week 4 Weight Category and Dose Group

	DB Adalimumab eow, n (%)			
	Weight < 40 kg		Weight ≥ 40 kg	
	10 mg dose N = 31	20 mg dose N = 29	20 mg dose N = 64	40 mg dose N = 64
Any adverse event	24 (77.4)	26 (89.7)	57 (89.1)	60 (93.8)
At least possibly drug-related[a]	11 (35.5)	9 (31.0)	26 (40.6)	30 (46.9)
Severe adverse event	4 (12.9)	9 (31.0)	7 (10.9)	10 (15.6)
Serious adverse event	4 (12.9)	10 (34.5)	15 (23.4)	12 (18.8)
Leading to discontinuation of study drug	3 (9.7)	8 (27.6)	9 (14.1)	7 (10.9)
At least possibly drug-related SAE[a]	0	0	2 (3.1)	1 (1.6)
Infectious adverse event	14 (45.2)	19 (65.5)	33 (51.6)	37 (57.8)
Serious infections	1 (3.2)	2 (6.9)	2 (3.1)	3 (4.7)
Malignancies	0	0	0	0
Lymphomas	0	0	0	0
NMSC	0	0	0	0
Malignancies (excluding NMSC and lymphomas)	0	0	0	0
Malignancies (including lymphomas, excluding NMSC)	0	0	0	0
Injection site reactions	2 (6.5)	1 (3.4)	8 (12.5)	8 (12.5)
Opportunistic infections, excluding TB	0	0	1 (1.6)	1 (1.6)
Congestive heart failure	0	0	0	0
Demyelinating disease	0	0	0	0
Hepatic-related adverse events	0	0	5 (7.8)	4 (6.3)
Allergic reactions	1 (3.2)	0	1 (1.6)	6 (9.4)
Lupus-like syndrome	0	0	0	0
Hematologic-related adverse events	1 (3.2)	3 (10.3)	3 (4.7)	6 (9.4)
Fatal AEs	0	0	0	0
Deaths[b]	0	0	0	0

(Source: Clinical Study Report for M06-806 Table 75, page 353)

4.3.3 Dose escalation

Subjects were expected to remain on blinded EOW therapy throughout the 48-week study period. However, at or after Week 12, subjects who experienced a disease flare (increase in the PCDAI of ≥ 15 points when compared to Week 4 and an absolute PCDAI score above 30) or were non-responders (not achieving a decrease in the PCDAI score of at least 15 points when compared to the Baseline score for 2 consecutive visits at least 2 weeks apart) could be switched from blinded EOW to blinded EW dosing, continuing with the same blinded dose. Subjects in the Low-Dose treatment group were more likely to dose escalate from EOW to EW compared to the High-Dose treatment group, i.e., odds ratio < 1.0, however no statistically significant difference was observed.

Table 22. Proportion of Subjects Who Dose-escalated from EOW to EW (ITT Analysis Set)

Adalimumab Low-Dose 20 mg or 10 mg n/N (%)	Adalimumab High-Dose 40 mg or 20 mg n/N (%)	Odds Ratio	95% CI	*P* value[a]
48/95 (50.5)	35/93 (37.6)	0.59	0.33, 1.06	0.076

(Source: Clinical Study Report for M06-806 Table 57, page 301)

Of subjects who dose-escalated, subjects in the High-Dose treatment group were more likely to achieve PCDAI clinical remission and clinical response at Week 52 compared with subjects in the Low-Dose treatment group.

Table 23. Proportion of Subjects Who Were in PCDAI Clinical Remission and Clinical Response at Week 52, by Dose Escalation (ITT Analysis Set)

	Adalimumab Low-Dose 20 mg or 10 mg n/N (%)	Adalimumab High-Dose 40 mg or 20 mg n/N (%)	Odds Ratio	95% CI	*P* value[a]
Not achieved PCDAI response prior to dose escalation					
Clinical remission	2/12 (16.7)	3/8 (37.5)	3.00	0.37, 24.17	0.302
Clinical response	4/12 (33.3)	3/8 (37.5)	1.20	0.19, 7.77	0.848
Achieved PCDAI response prior to dose escalation					
Clinical remission	7/36 (19.4)	8/27 (29.6)	1.74	0.54, 5.61	0.350
Clinical response	19/36 (52.8)	17/27 (63.0)	1.52	0.55, 4.21	0.420
Overall					
Clinical remission	9/48 (18.8)	11/35 (31.4)	1.99	0.72, 5.49	0.186
Clinical response	23/48 (47.9)	20/35 (57.1)	1.45	0.60, 3.48	0.407

(Source: Clinical Study Report for M06-806 Table 58, page 302)

***Reviewer's comment**: Although CDAI clinical remission following 40 mg EW dosing was not significantly different from that with 40 mg EOW dosing in adults (Study M06-404), increasing dose frequency to patients with a disease flare or non-responders appear to be beneficial to some patients as 16.7% of patients in Low-Dose group and 37.5% of patients in High-Dose group showed clinical remission at Week 52 while they did not achieve clinical response prior to dose escalation. Also among patients who achieved clinical response prior to dose escalation, the clinical remission at Week 52 was 19.4% in Low-Dose group and 29.6% in High-Dose group.*

4.3.4 Population PK modeling

The estimated PK parameters and their associated variability for the adalimumab base model are listed in Table 24.

Table 24. Population PK Parameters Estimates

Parameter	Population Estimate (SEE)	%RSE	95% CI
CL/F (L/day)	0.288 (0.013)	4.55	0.262 – 0.314
V_2/F (L)	4.35 (0.280)	6.44	3.80 – 4.90
k_a (1/day)	0.202 (0.025)	12.5	0.152 – 0.252
(%CV*) Inter-Ind. Variab. – CL	0.253 (50.30)	NA	NA
Residual Error Term – Proportional	0.096	NA	NA
Residual Error Term – Additive	1.38	NA	NA

(Source: Population PK Exposure- Response Report Table 2)

As shown in Figure 12, body weight and AAA status appeared to have high correlation with apparent clearance of adalimumab.

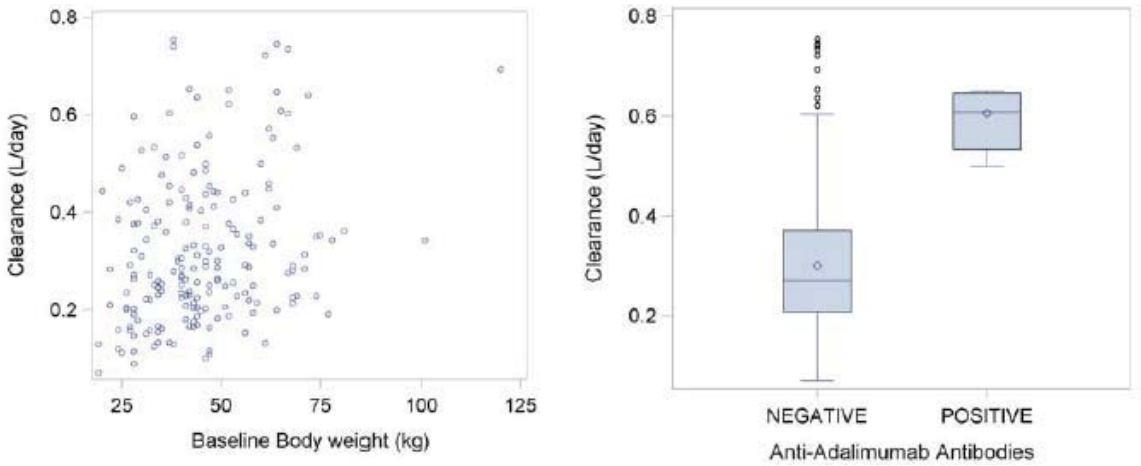

Figure 12. CL/F versus covariates body weight and AAA status (Base model)

(Source: Population PK Exposure- Response Report Figure 4)

The final model was a one-compartment with one exponential term for inter-individual variability on apparent clearance. The covariate model for clearance included baseline body weight and the occurrence of anti-adalimumab antibodies (AAA). The covariate model for central volume (V2/F) included baseline body weight. The time-dependent influence of body weight on the PK parameters was observed to be minor, thus baseline

body weight was selected as the model covariate. Combined error model was found to be most appropriate for explaining the residual error.

$$CL = \theta_1 \times (1 + \theta_5 \times AAA) \times \left(\frac{WTBS}{Median(WTBS)} \right)^{\theta_4} \times \exp(\eta_1)$$

$$V2 = \theta_2 \times \left(\frac{WTBS}{Median(WTBS)} \right)^{\theta_6}$$

Table 25. Parameter estimates and variability for adalimumab PK (Final model)

Parameter	Population Estimate (SEE)	%RSE	95% CI
CL/F (L/day)	0.281 (0.011)	4.06	0.259 – 0.303
V_2/F (L)	4.75 (0.195)	4.11	4.37 – 5.13
k_a (1/day)	0.200 (0.013)	6.70	0.174 – 0.226
Covariate WTBS on CL/F	0.480 (0.115)	24.0	0.255 – 0.705
Covariate AAA on CL/F	1.08 (0.130)	12.0	0.825 – 1.34
Covariate WTBS on V_2/F	0.904 (0.086)	9.55	0.735 – 1.07
(%CV*) Inter-Ind. Variab. – CL	0.211 (45.9)	NA	NA
Residual Error Term – Proportional	0.071	NA	NA
Residual Error Term – Additive	1.900	NA	NA

(Source: Population PK Exposure- Response Report Table 3)

Inter-individual variability for adalimumab CL/F was ~46%. The goodness-of-fit for the final model (Figure 13) and visual predictive check (not shown) indicate the final model appears to describe the data adequately. There was ~69% increase in median CL/F from the lowest body weight quartile of 19 to 34 kg to the highest weight quartile of 54 to 120 kg. The median values for CL/F were comparable for subjects < 13 years of age (10.23 mL/h) compared to subjects ≥13 years of age (12.74 mL/h). Median CL/F was about 2.5-fold higher in the AAA+ subjects versus AAA- subjects. Six subjects among 189 patients were AAA+ in the current study.

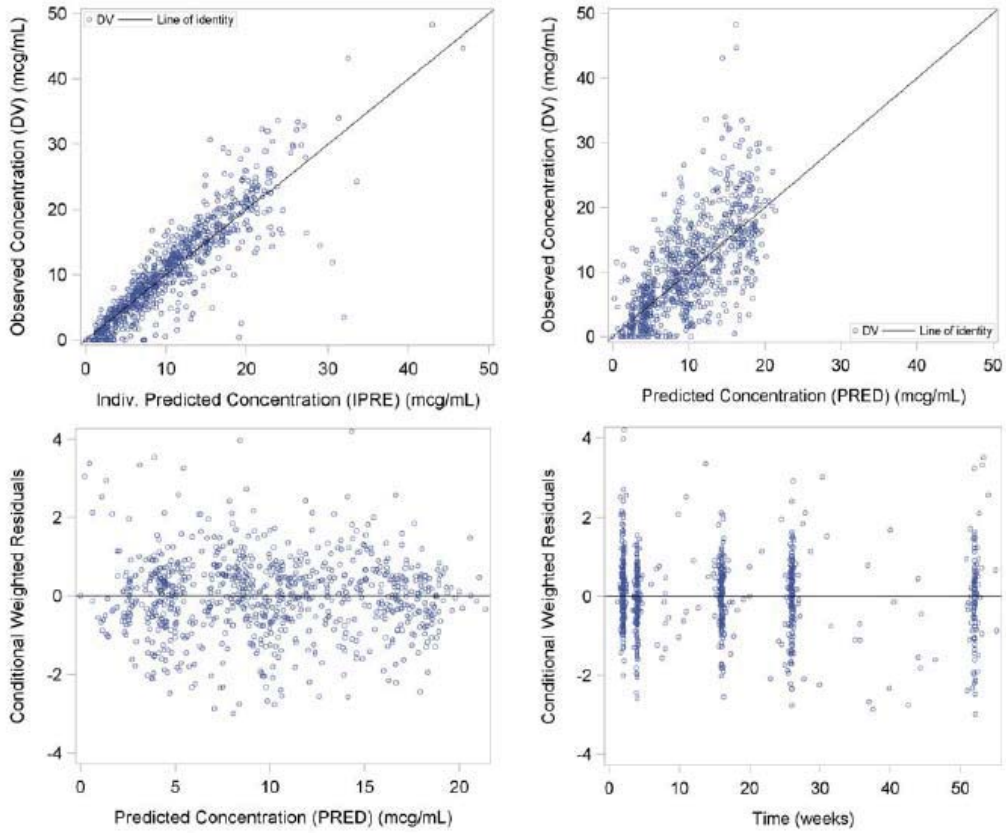

Figure 13. Goodness-of-fit *(Source: Population PK Exposure-Response Report Figure 6)*

4.3.5 Markov Chain Exposure-Response Modeling

A continuous-time Markov model was employed to describe the time course of adalimumab concentration effect on clinical outcome state transition rates. A base model that defined the structural model was as shown in Figure 14.

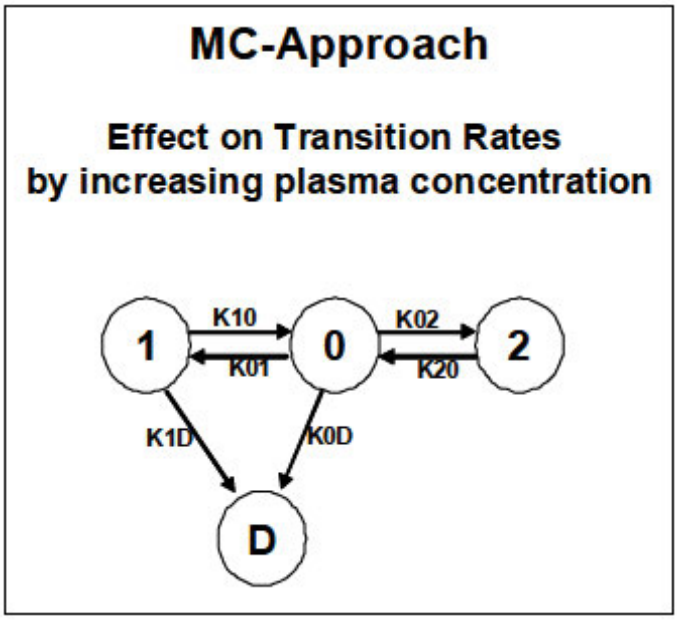

Figure 14. Continuous Time Markov Model

The course of disease was modelled via transitions between model states which were characterized by respective probabilities Pij. Due to the time-continuous implementation, rapid changes of disease states were enabled. Occurrence of multiple flares could also be accounted for by several transitions to and from the flare state.

The stochastic process was described by the Kolmogorov backward equation, yielding a system of differential equations for the probabilities of going from state i to state j.

$$\frac{dP_{ij}}{dt} = \sum_{s \neq j} K_{is} * P_{sj}(t) - \sum_{s \neq j} K_{is} * P_{ij}(t)$$

The common logarithm of each transition rate was estimated on account of numerical stability.

$$K_{10} = 10^{tK_{10}}$$

$$K_{02} = 10^{tK_{02}}$$

$$K_{0D} = 10^{tK0D}$$

$$K_{1D} = 10^{tK1D}$$

Drug effect was incorporated by inhibiting the transition to worse states (k01 0 →1, k20 2→0) via a drug dependent maximum effect (Emax) function.

$$K_{01} = 10^{tK_{01}} \bullet \left(1 - \frac{Conc}{Conc + EC_{50}} \bullet E_{max}\right)$$

$$K_{20} = 10^{tK_{20}} \bullet \left(1 - \frac{Conc}{Conc + EC_{50}} \bullet E_{max}\right)$$

The model was optimized by minimizing twice the negative log-likelihood of the sum over transition probabilities Pij given observations Pi, where i depicted the current state and j the previous state.

$$P_j(t) = \sum_{0}^{i=j} P_i \bullet P_{ij}$$

The continuous time Markov model is a probabilistic method for mean representation. Accordingly, intra-individual variation does not apply, resulting in the absence of a residual error model (EPS) in Table 26. The modeling exercise was based on direct optimization of the likelihood. This was done by specifying the LIKE option in the NONMEM $ESTIMATION block. The covariates effect on EC_{50} was investigated in both models. The final model included prior infliximab use (INFB) and concomitant corticosteroids (CORT) as covariates on EC_{50}. The model estimated EC_{50} values was log10 (0.566) or 3.68 mcg/mL.

Table 26. Final Model Parameter Estimates and Variability for the Markov Model Based Exposure-Response Relationship

Parameter	Population Estimate (SEE)	%SE	95% Confidence Interval	95% Confidence Interval (de-log10)
log10(EC_{50})(µg/mL)	0.566 (0.170)	30.0	0.233 – 0.899	1.71 – 7.93
E_{Max}	1(FIX)	--	--	--
log10(K_{01}(1/day))	–1.50 (0.123)	–8.20	–1.74 – (1.26)	0.018 – 0.055
log10(K_{10}(1/day))	–1.12 (0.108)	–9.64	–1.33 – (0.908)	0.047 – 0.124
log10(K_{02}(1/day))	–1.88 (0.042)	–2.22	–1.96 – (1.80)	0.011 – 0.016
log10(K_{20}(1/day))	–1.64 (0.095)	–5.77	–1.83 – (1.46)	0.015 – 0.035
log10(K_{0D}(1/day))	–2.46 (0.096)	–3.90	–2.65 – (2.27)	0.002 – 0.005
log10(K_{1D}(1/day))	–1.80 (0.128)	–7.11	–2.05 – (1.55)	0.009 – 0.028
Dropout Factor	1.18 (0.063)	5.33	1.06 – 1.30	NA
INFB on EC_{50}	0.582 (0.188)	32.3	0.214 – 0.950	1.64 – 8.92
CORT on EC_{50}	0.377 (0.180)	47.8	0.024 – 0.730	1.06 – 5.37

(Source: Population PK Exposure-Response Report Table 10)

Goodness-of-fit plots are not feasible for assessing quality of categorical models with Morkovian elements. Because the transition from one state to the next is dependent on the previous state, NONMEM uses the observed data to predict the next state, marking an unbiased assessment of VPCs difficult. Therefore, in order to assess the appropriateness of the model by visual predictive checks, it was transferred to Trial Simulator to obtain data independent simulations.

The Trial Simulator based visual predictive checks (N=1000 replicates) for response (%Remission)-time profiles and overall 1 drop out (%Drop Out)-time profiles for adalimumab are presented in Figure 15.

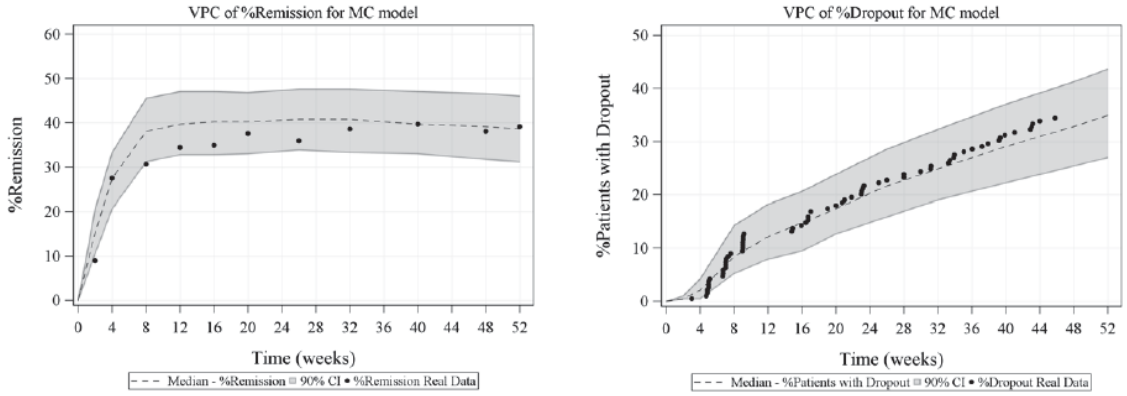

Figure 15. Exposure-Response Visual Predictive Checks for %Subjects in Remission (Left) and % Subjects who Dropped Out (Right) in Study M06-806

(Source: Population PK Exposure-Response Report Figure 8)

Reviewer's comments: The reviewer's independent exposure-response analysis with observed trough concentrations and clinical endpoints such as clinical remission at Week 26, instead of the applicant's PD model, was utilized for the regulatory decision.

4.3.6 Simulations for Splitting the Induction Dose over One

In Study M06-806, the induction dose regimen consisted of a fixed dose of 160 mg (≥40 kg, high-dose) administered at Week 0 and 80 mg at Week 2. The induction doses were administered as consecutive injections in a single day, that is, 4 injections for the 160 mg dose and 2 injections for the 80 mg dose. Multiple injections in 1 day may be difficult for pediatric subjects to tolerate therefore; an alternative induction dosing regimen was evaluated.

Current regimen was dosed as 160 mg on Day 0 and 80 mg on Day 14. Simulated alternative regimen involving splitting the 160 mg dose over 2 days is shown below.

		Treatment Days		
		Day 0	Day 1	Day 14
Scenario	Current	160	--	80
	Simulation 1	80	80	80

The results showed that the serum concentrations of adalimumab generally overlap between the simulated alternative regimen and the current regimen.

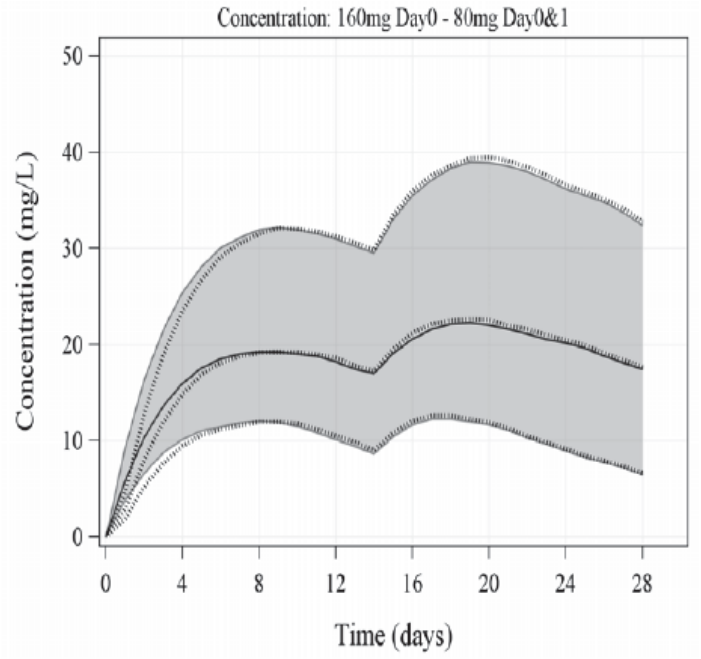

Figure 16. Comparisons of simulated serum mean concentrations of 160 mg adalimumab given over 1 or 2 days. *(Source: Population PK Exposure-Response Report Figure 12)*

The sponsor performed simulations further to evaluate dose escalation, to compare body weight based dose regimens and fixed dose regimens with body weight cutoff of 30 kg or 40 kg. From those exercises, the sponsor concluded that dose escalation from 20/10 mg EOW to 40/20 mg EOW or 20/10 mg EW, achieved comparable exposure, and the body weight based dose regimen does not appear to have advantage over fixed dose regimen with body weight cut-off of 40 kg.

***Reviewer's comments**: Splitting the induction dose of 160 mg into two 80 mg consecutive dosing over 2 days were already approved for adults based on the applicant's similar simulation. Splitting the induction dose of 160 mg into two 80 mg consecutive dosing over 2 days appears to be reasonable.*

5 REVIEWER'S ANALYSIS

5.1 Introduction

The sponsor's analysis was based on dose groups (High Dose and Low Dose) for both body weight groups (≥ 40 kg and < 40 kg) and subgroup analysis by body weight group was not conducted. Thus, reviewer conducted subgroup analysis for the primary efficacy endpoint and high ranked secondary efficacy endpoints. Exposure-response analysis along with dose-response analysis for both induction phase and maintenance phase were conducted to evaluate the adequacy of the proposed dosing regimen in the target population.

5.2 Objectives

Analysis objectives are:

1. To analyze exposure-response relationship for efficacy endpoints including PCDAI clinical remission at Week 26 within pediatric patients by both dose and body weight groups
2. To find risk factors associated with low exposure and low efficacy for dose optimization

5.3 Methods

5.3.1 Data sets

Data sets used in the analysis are summarized in **Table 27**. For PCDAI profiles, ITT dataset was utilized (N=189). Among them, 4 subjects did not receive protocol-specified doses so they were excluded from the analysis dataset (N=185). For other analyses, per protocol dataset (N=179) was utilized. One patient (SUBJID (b) (6)) was found to have received 40 mg at Baseline, thus removed from the analysis dataset (N=178). For exposure-response analysis for Week 26, patients who stayed with EOW dosing until Week 26 PCDAI assessment were only included in the analysis dataset (N=133). Among them, trough concentrations at Week 26 were available only in 90 patients. For the analysis for Week 52, only patients who dose was not escalated during the study were included (N=98). Among them, only 65 patients' trough concentrations at Week 52 were available.

Table 27. Analysis Data Sets

Study Number	Name	Link to EDR
pcdai.xpt dmbl.xpt eff404.xpt		\\cdsesub1\bla\eCTD_Submissions\STN125057\0234\m5\datasets\m06-806\analysis\legacy\datasets

pk.xpt		\\cdsesub1\bla\eCTD_Submissions\STN125057\0234\m5\datasets\m06-806\tabulations\legacy
Pop-pk-model-dataset.xpt		\\cdsesub1\bla\eCTD_Submissions\STN125057\0252\m5\datasets\m06-806\analysis\legacy\datasets

5.3.2 Software

Population pharmacokinetics modeling was performed with NONMEM (version 7.2) and graphical, statistical analysis and simulation were performed with R (version 2.13.1).

5.3.3 PCDAI clinical remission

To evaluate overall response to adalimumab in each treatment group, the profiles of PCDAI score were plotted against time (Figure 17). The increasing trends in median PCDAI score were observed in 3 treatment groups except 40 mg in BW ≥ 40 kg. Overall profiles show that the clinical remission in High Dose group is consistently higher than that in Low Dose group as odds ratio between High Dose and Low Dose were consistently higher during the maintenance period (Table 28).

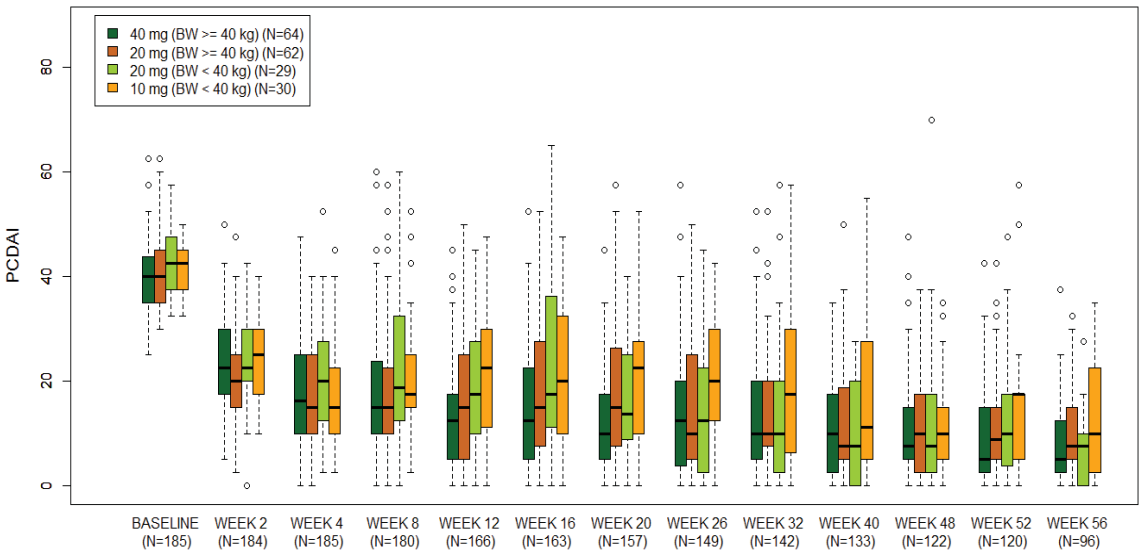

Figure 17. PCDAI by treatment group

Table 28. PCDAI Clinical Remission over Time by Dose Group

Visit	Low Dose	High Dose	OR (95% CI)	p-value
Week 4	29/95 (30%)	23/93 (24.7%)	0.75 (0.39, 1.42)	0.375

Week 8	32/95 (33.7%)	27/93 (29.0%)	0.81 (0.43, 1.49)	0.492
Week 12	32/95 (33.7%)	34/93 (36.6%)	1.13 (0.62, 2.07)	0.680
Week 16	31/95 (32.6%)	32/93 (34.4%)	1.08 (0.59, 1.98)	0.796
Week 20	28/95 (29.5%)	39/93 (41.9%)	1.73 (0.95, 3.16)	0.076
Week 26	27/95 (28.4%)	36/93 (38.7%)	1.59 (0.86, 2.93)	0.136
Week 32	26/95 (27.4%)	38/94 (40.9%)	1.83 (0.99, 3.38)	0.052
Week 40	22/95 (23.2%)	34/93 (36.6%)	1.91 (1.01, 3.61)	0.046*
Week 48	22/95 (23.2%)	35/93 (37.6%)	2.00 (1.06, 3.78)	0.032*
Week 52	22/95 (23.2%)	31/93 (33.3%)	1.66 (0.87, 3.15)	0.123

(S*ource: M06-806 CSR Table 44*)

5.3.4 Exposure-Response for Induction Phase

Among exposure-response analysis dataset, concentration data at Week 4 were available for 167 patients. From the analysis with this subset of data, there was no apparent exposure-response relationship or dose-response relationship observed during the induction phase (Figure 3). Since only one dose was chosen for each group stratified by body weight (≥ 40 kg or < 40 kg), a reasonable conclusion we could make from this analysis is that clinical remissions at Week are comparable between patients with body weight ≥ 40 kg following 160 mg on Day 1 and 80 mg on Day 14 and patients with body weight < 40 kg following 80 mg on Day 1 and 40 mg on Day 14.

5.3.5 Exposure-Response for Maintenance Phase

An apparent exposure-response relationship for PCDAI at Week 26 was observed as shown in Figure 2 and the adalimumab concentration and the clinical remission at Week 26 for each quartile are summarized in Table 2. As concentration increases from Q1 to Q4, clinical remission increases from 34.8% to 73.9%. The highest quartile (Q4) appears to be close to plateau in the exposure-response curve, and patients whose trough concentrations < 5 mcg/mL showed lower remission. Considering that mean (±SD) trough concentration in adults (Study M06-433) following 40 mg EOW dosing regimen was 6.81 (±4.32) mcg/mL at Week 24 and 7.61 (±4.97) mcg/mL at Week 52, targeting exposure to Q3 (7.4 mcg/mL) in pediatric population might be appropriate.

Table 29. Summary of Mean Trough Concentration and PCDAI Clinical Remission at Week 25 by Quartile of Concentration of Adalimumab and by Treatment Group

	Subgroup	Ctrough (Mean ± SD)	Clinical Remission at Week 26
All (N=91)	**Q1 (N=23)**	0.95 ± 0.73	8/23 (34.8% [15.3, 54.2]
	Q2 (N=22)	4.07 ± 0.91	12/22 (54.5% [33.7, 75.4]
	Q3 (N=23)	7.4 ± 1.13	16/23 (69.6% [50.8, 88.4]
	Q4 (N=23)	13.4 ± 3.25	17/23 (73.9% [56.0, 91.9]
< 40 kg (N=24)	**10 mg (N=14)**	1.98 ± 1.41	5/14 (35.7% [10.6, 60.8]
	20 mg (N=10)	7.57 ± 3.62	7/10 (70% [41.6, 98.4]
≥ 40 kg (N=67)	**20 mg (N=33)**	3.7 ± 2.71	20/33 (60.6% [43.9, 77.3]
	40 mg (N=34)	10.7 ± 4.6	21/34 (61.8% [45.4, 78.1]

The exposure-response with all datasets (ER dataset II; N=133 including 42 patients who miss data for concentration data at Week 26) are shown in Table 29. It is clear that trough concentrations following low doses are below the mean concentration of Q3, suggesting these low doses are unlikely optimal doses in the target population. Patients in the lowest quartile (Q1) were mainly stemmed from low dose groups (10 mg for body weight < 40 kg and 20 mg for body weight ≥40 kg) as shown in Figure 6. Proportion of patients who were in Low Dose group in the lower quartiles of Q1 and Q2 was 91% and 82%, respectively (Figure 6 and Table 6). Significant portion of patients of the Low Dose group in lower quartiles (Q1 and Q2) support High Dose for higher clinical remission.

Furthermore, the higher efficacy of high dose in both body weight groups are consistently observed with secondary endpoints: clinical response at Week 26, clinical remission at Week 52 and clinical response at Week 52 (Table 5), suggesting high dose is optimal for maintenance of therapy.

5.3.5.1 Risk factors in quartiles

To evaluate any risk factors associated with lower exposure which potentially cause lower efficacy, analyses with key variables for baseline characteristics were conducted (Figure 6 and Table 6). Greater number of male patients was included in the lowest quartile and greater number of female patients was included in the highest quartile. Substantial portion of patients in the two lower quartiles (Q1 and Q2) had baseline CRP ≥ 1.0 mg/dL. The baseline PCDAI score also tends to be higher in the lower quartiles as well.

However, the interpretation for causality relationship is not feasible because dose is confounded by some key baseline characteristics such as baseline PCDAI. To evaluate if these risk factors are likely associated with low exposure or arisen from lack of randomization in treatment group, a similar analysis was conducted for treatment group with per protocol data set (N=178). As shown in Figure 18, significant portion of patients in treatment group with body weight < 40 kg had CRP ≥1.0 mg/dL and Baseline PCDAI score ≥ 40. The disease condition in patients with body weight < 40 kg were worse than those with body weight ≥40 kg, and tend to produce lower concentration of adalimumab which might have caused lower efficacy. However, these patients received half of the dose given to the patients with body weight ≥ 40 kg, thus it is difficult to tease out the effect of baseline disease condition from the effect of dose.

(b) (4)

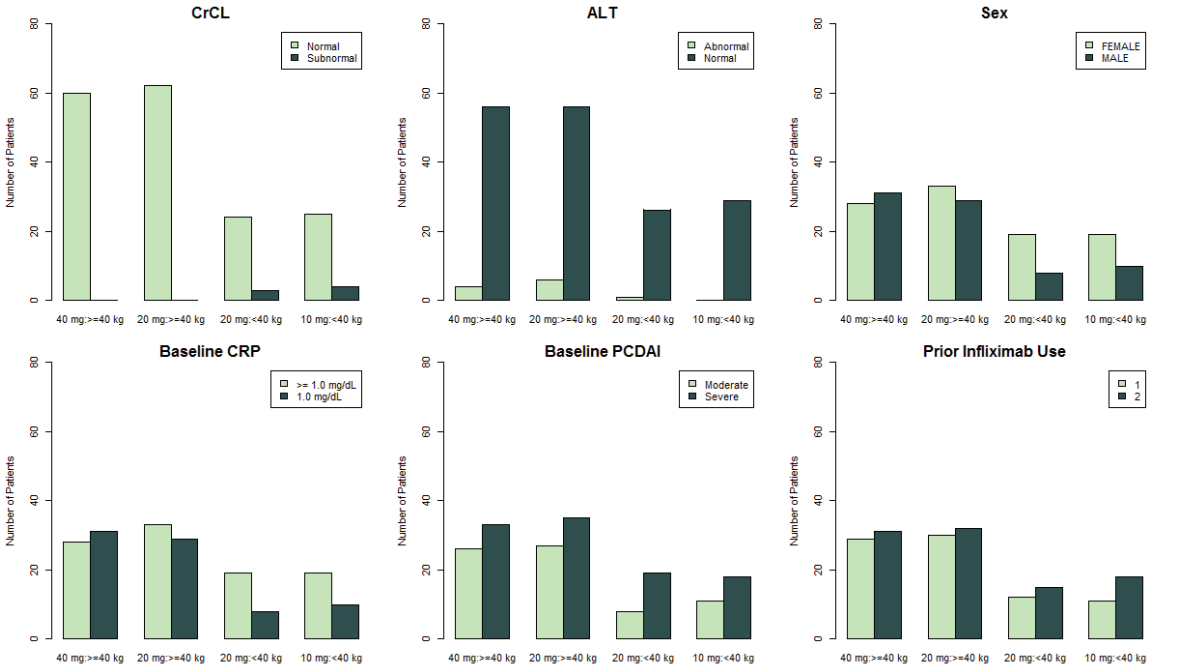

Figure 18. Baseline risk factors in treatment group (N=178)

Table 30. Risk factors in each treatment group (N=178)

	CrCL < 80 mL/min	ALT ≥ 30	Female	Baseline CRP ≥ 1.0 mg/dL*	Baseline PCDAI ≥ 40*	Prior INFB Use

40 mg ≥ 40kg (N=60)	0	4 (7%)	27 (45%)	28 (47%)	33 (55%)	29 (48%)
20 mg ≥ 40 kg (N=62)	0	6 (10%)	30 (48%)	33 (53%)	35 (56%)	30 (48%)
20 mg < 40 kg (N=27)	3 (11%)	1 (4%)	12 (44%)	19 (70%)	19 (70%)	12 (44%)
10 mg < 40 kg (N=29)	4 (14%)	0	10 (35%)	19 (66%)	18 (62%)	11 (38%)

5.3.6 Dose escalation

Dose escalation from EOW to EW to patients with a disease flare or who do not achieve clinical response at Week 26 was included in the protocol. These patients, who dose escalated, however, were considered non-responders for the primary efficacy endpoint. Nonetheless, substantial portion of patients did have dose escalation, and the proportion of subjects who received escalated dose was greater in low dose groups, especially for the patients with body weight < 40 kg (Table 10).

Causes for the lack of response or a disease flare that led to dose escalation appear to be combination of multiple factors. First of all, low exposure due to low dose and/or high clearance seems to be influential. Apparently higher clearance is associated with dose escalation, body weight and disease severity (Figure 19).

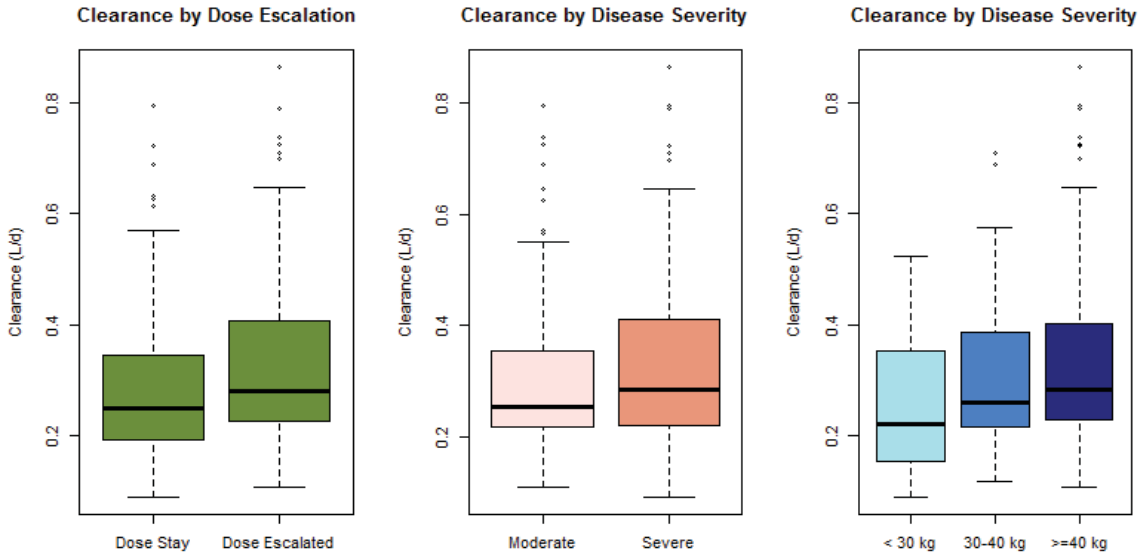

Figure 19. Comparison of apparent clearance by dose escalation, disease severity and body weight

As shown in Figure 10 (20 mg in BW < 40 kg and 10 mg in BW < 40 kg), adalimumab concentrations in patients who dose escalated tend to be lower compared to those in patients who stayed with EOW dosing regimen prior to Week 12. However, adalimumab concentration prior to dose escalation is not significantly lower in patients with body weight ≥ 40 kg who escalated dose compared to the patients who did not. Since time for occurrence of dose escalation varies by patients, individual response to dose escalation was explored to understand the effect of dose escalation (Figure 11). As shown in Figure 11, some patients show benefit upon dose escalation from EOW to EW dosing, suggesting a potential benefit of dose escalation to in patients who exhibit inadequate response or flare during the course of the therapy.

6 LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
ER Analysis for Humira pediatrics.R	PKPD analysis Exposure-Response for efficacy	Reviews\Ongoing PM Reviews\Adalimumab

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/s/

JEE E LEE
08/21/2014

YOW-MING C WANG
08/21/2014
My sigature represents (1) my concurrence in the role of a secondary reviewer of DCP3 and (2) the concurrence of the DCP3 primary reviewer, Dr. Jie Wang, because he is currently unable to access DARRTS due to technical issues.

NITIN MEHROTRA
08/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125057Orig1s356

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Monoclonal Antibodies
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date:	September 12, 2014
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Division of Monoclonal Antibodies
Through:	Jun Park, PhD, Product Quality Reviewer Laurie Graham, MS, Team Leader Division of Monoclonal Antibodies
Application:	BLA 125057/356
Product:	Humira (adalimumab)
Applicant:	AbbVie Inc.
Submission Dates:	August 29, 2013

Executive Summary

The carton and container labels for Humira (adalimumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, [8/1/2014 to 11/30/2014]. The container label and carton labeling submitted on August 29, 2013 are acceptable.

Background and Summary Description

BLA 125057/356 is an efficacy supplement that provides for a proposed indication for Pediatric Crohn's disease for pediatric patients 6 years of age and older. This new dosage includes induction regimens (160 mg/80 mg or 80 mg/40 mg) and maintenance doses (10 mg or 20 mg every other week). To support the new indication, the Applicant proposed a 10 mg prefilled syringe (PFS), along with two new start packs for the induction regimens.

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling along a Human Factors Study. DMEPA's May 16, 2014 review recommended revising the image of the PFS on the carton labeling.

Materials Reviewed:

- Container Label, 10 mg PFS
- Inner Tray Carton Labeling, 10 mg PFS
- Outer Carton Labeling, 10 mg PFS 2-count
- Carton Labeling, 10 mg PFS, Starter Pack 3-count
- Carton Labeling, 10 mg PFS, Starter Pack 6-count
- Inner Tray Carton Labeling, 20 mg (trade and sample)
- Outer Carton Labeling, 20 mg 2-count (trade and sample)

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Start of Sponsor Material

Container Label, 10 mg PFS

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Review

Overall, the Applicant formatted the proposed labels and labeling similar to the currently approved labels and labeling. We identified the following concerns.

Inactive Ingredients

The inactive ingredients are not listed in alphabetical order per USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1091> Labeling of Inactive Ingredients. However, the proposed presentation is acceptable for the following reasons:

- Humira is currently marketed in multiple package configurations that have undergone Human Factors Studies and found to be acceptable from a safety perspective.
- Alphabetical listing of inactive ingredients is not a mandatory requirement from USP but rather a CDER preference.

Lot and Expiration Date

There is no lot and expiration date noted on all proposed carton labeling. Upon review of the approved carton labeling, there is no lot and expiration noted. It is likely that when the Applicant prints the labeling, the lot and expiration date appear but not do not appear on the proposed mockup.

FDA Request: Confirm the expiration and lot number date to comply with 21 CFR 610.61(c), 21 CFR 610.61(d), and 21 CFR 201.17. The expiration date and lot number do not appear on the draft labeling submitted to this S-356.

AbbVie Response:
The expiration date and lot number are variable data that is printed online at the manufacturing plant. It is printed on an area of the carton and lidding stock (tray labeling) that is unvarnished, unprinted, and free of graphics. The expiration date and lot number are not part of the carton graphics or lidding stock (tray labeling) preprinted copy and therefore are not on the graphics submitted to S-356. The expiration and lot number complies with 21 CFR 610.61(c), 21 CFR 610.61(d), and 21 CFR 201.17.

FDA Response: Acceptable.

Visual Inspection:

The Applicant states the formulation and container closure for the proposed PFS is identical to the approved PFS except for the fill volume. However, it is unclear whether sufficient area on the syringe remains uncovered for its full length or circumference to permit visual inspection of the contents per 21 CFR 610.60(e).

FDA Request: Confirm that once the label is affixed to the syringe, sufficient area on the syringe remains uncovered for its full length or circumference to permit visual inspection of the contents per 21 CFR 610.60(e).

AbbVie Response:
The prefilled syringe container label is a clear label that is affixed to the barrel of the syringe. Sufficient area on the syringe remains uncovered to permit visual inspection of the contents per 21 CFR 610.60(e).

FDA Response: Acceptable.

Conclusions

The container label and carton labeling submitted on August 29, 2013 are acceptable.

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/s/

JIBRIL ABDUS-SAMAD
09/15/2014

LAURIE J GRAHAM
09/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Review

*** This document contains proprietary information that cannot be released to the public***

DATE: August 24, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Matthew Brancazio, Regulatory Project Manager, CDER/OND/ODEIII/DGIEP

SUBJECT: **sBLA 125057/356**
Applicant: AbbVie Inc
Device Constituent: Prefilled Syringe
Drug Constituent: Humira
Intended Treatment: Crohn's disease
CDRH CTS Tracking No. 1300533

Digitally signed by Quynhnhu T. Nguyen -S
Date: 2014.08.27 13:45:35 -04'00'

QuynhNhu Nguyen, Combination Products Human Factors Specialist
(Human Factors Premarket Evaluation Team - HFPMET)

Ronald D. Kaye -S
Digitally signed by Ronald D. Kaye -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ronald D. Kaye -S, 0.9.2342.19200300.100.1.1=1300110677
Date: 2014.08.27 15:08:30 -04'00'

Ron Kaye, Human Factors and Device Use-Safety Team Leader (HFPMET)

DRH Human Factors Review

Overview and Recommendation

The Division of Gastroenterology and Inborn Errors Products, Office of New Drugs, Center for Drug Evaluation and Research, requested CRH Human Factors Premarket Evaluation Team (HFPMET) consultative review of the sBLA 125057/356 (submission receipt date 8/29/2013). The purpose of this submission is to submit an efficacy supplement for a new indication for adalimumab. The proposed indication is "HUMIRA® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4)
To support the dosing of this indication, a newly developed 10 mg PFS is introduced in this supplement. The formulation and container closure of the drug product in the 10 mg/0.2mL PFS presentation is identical to the approved Humira presentations.

Two study reports were included in this supplement of the BLA: (1) Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report; and (2) Dosing Comprehension for Humira for Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report.

The Pharmacist and Pharmacy Technician Human Factors Validation Study Report showed errors and close calls where the pharmacy technician cohort dispensed incorrect medication or would have dispensed incorrect medication if the pharmacists did not correct the errors respectively. For those errors that were not corrected by the pharmacists, we are most concerned with errors where the technicians dispensed Humira pens instead of Crohn's disease starter package, adult starter package instead of pediatric package, and small pediatric starter package instead of large pediatric starter package. We believe that if these errors were to occur in actual use, they could lead to delay of therapy or sub-optimal treatment. The Patients and Caregivers Validation Study Report showed 1 participant failed to complete all three tasks (initial dose, second dose, and maintenance dose), 2 participants failed to complete task 2, and 1 participant failed to complete task 3. We are concerned that these errors can result in sub-optimal treatment (i.e., underdose and overdose).

Based on these study results, several information requests (IRs) were issued to Abbvie and a response was received on 3/17/2014. For the Pharmacist and Pharmacy Technician Human Factors Validation Study, Abbvie (1) provided copies of all prescriptions that were used in the study, (2) clarified the differences between the packaging of the commercially available Humira products and the packaging of the proposed product, (3) discussed the clinical impact on user making packaging selection errors, (4) supplied additional subjective data which revealed that the errors and close calls observed were not found to be directly related to the product packages or package designs, (5) provided a discussion on how the product labeling has been optimized to ensure safe and effective use.

For the Patients and Caregivers Validation Study, Abbvie provided updated product labeling including Instructions for Use for patients to address the concern that participants did not review the Starter Package Information and Calendar. In addition, Abbvie supplied additional subjective data which indicated that the errors observed were not found to be directly related to

the Starter Package labeling. Abbvie believes that the dosing instructions for the PCD Starter Packages have been optimized in particular; the Starter Package contains an example calendar, which was tested during the human factors validation study and contains dosing instructions to assist the patient with induction dosing.

Given the additional information that Abbvie provided in their response, it appears that the root cause analysis of the subjective data from study participants indicated that the use errors were not found to be related to the product labeling. Even so, Abbvie intends to further optimize product labeling including the Instructions for Use for patients to address FDA's concern that participants did not review the Starter Package Information and Calendar. This human factors reviewer found Abbvie's response to be acceptable and did not have any further questions regarding the human factors study results.

CDRH Human Factors Review

Combination Product Device Information

Submission No.: sBLA 125057/356
Applicant: AbbVie Inc
Device Constituent: prefilled syringe
Drug Constituent: Humira
Intended Treatment: Crohn's disease (CD)

CDRH Human Factors Involvement History

- 8/29/2014: CDRH HFPMET received a request to review human factors validation study report
- 2/6/2014: CDRH HFPMET provided CDER additional information requests to be issued to the Sponsor
- 4/3/2014: CDRH HFPMET was informed that the goal date for the submission has been extended, and the primary review due date is 8/24/2014
- 8/27/2014: CDRH HFPMET provided review recommendation to CDER

Summary of Human Factors Related Information

Two study reports were included in this supplement of the BLA: (1) Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report; and (2) Dosing Comprehension for Humira for Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report.

Study (1) was conducted with 15 specialty pharmacists and 15 specialty pharmacy technicians working in pairs. This study was designed to evaluate user ability to successfully fill prescriptions without selection error across a range of packages including the packages introduced with the Humira Pediatric Crohn's Disease indication (2 new starter packages and a 10 mg prefilled syringe package), and other commercially available Humira packages. A total of 117 prescriptions were filled. Below is a summary of the failures that were observed in the study:

- 1 technician filled order for adult CD Starter Package (6x40mg Pens) with 3 cartons of Humira 40mg Pens. Pharmacist did not correct.
- 1 technician filled order for 40mg Pen with 40mg Syringe. Pharmacist did not correct.
- 1 technician filled order for Large Starter Package (6x40mg Syringes) with Small Starter Package (3x40mg Syringes). Pharmacist did not correct.
- 1 technician filled order for Large Starter Package (6x40mg Syringes) with Adult CD Starter Kit (6x40mg Pens). Pharmacist did not correct.

Study (2) was conducted 22 participants consisting of parents and caregivers of children/adolescents with a chronic or critical medical condition representative of CD. This study was designed to demonstrate that the instructions for use could be comprehended by these users and that the users can identify the correct day to administer Dose 2 and first maintenance dose each 2 weeks apart. Two Starter Packs were used: Small Box (intended for children weighing under 40kg) and Large Box (intended for children weighing greater than or equal to 40kg). There were three study tasks which involved having the users identifying the correct number of doses for Initial Dose, Dose 2, and Maintenance Dose. A total of 6 failures were observed:

- 1 participant failed all three tasks
- 2 participants failed task 2 (Dose 2)
- 1 participant failed task 3 (maintenance dose)

Based on these results, several information requests (IRs) were issued to Abbvie. The following section provides the IR requests, and summary of Abbvie's response:

1. The Pharmacist and Pharmacy Technician Human Factors Validation Study Report showed errors and close calls where the pharmacy technician cohort dispensed incorrect medication or would have dispensed incorrect medication if the pharmacists did not correct the errors respectively. For those errors that were not corrected by the pharmacists, we are most concerned with errors where the technicians dispensed Humira pens instead of Crohn's disease starter package, adult starter package instead of pediatric package, and small pediatric starter package instead of large pediatric starter package. We believe that if these errors were to occur in actual use, they could lead to delay of therapy or sub-optimal treatment. Please address the following:
   a. Provide a copy of all of the prescriptions that were used in the study.
      Summary of Response: A copy of the prescriptions that were used in the human factors validation study is provided in Module 1.14.1.4 of this submission. The four types of prescriptions used in the study were: specialty pharmacy patient intake forms (78), phoned-in prescriptions (26), handwritten prescriptions (13), and handwritten prescriptions with missing information (9).
   b. Clarify the differences between the packaging of the currently marketed Humira products and the packaging of the proposed product. You may consider submitting this information in a table format.
      Summary of Response: Pictures of the commercially available Humira container artwork were previously submitted in the sBLA on 28 February 2014 (Sequence 0274). There are a number of distinct differences across Humira packaging, including package size, colors, inverted font for dose, increased font size for dose on the side panel, artistic style, NDC codes, and package opening format (Table 1).

Table 1. Summary of Humira Package Design Differences

Package Content and Dose	On Market?	Package Format	Package Dimensions (in) W × L × H	Package Volume (in^3)	Artistic Style	Package Primary Color	Package Secondary Color	Package Accent Color	Reversed Back-ground for Dose	Large Text Dose Side Panel
Humira 2 Pens Package 40 mg/0.8 mL NDC 0074-4339-02[a]	Yes	Top Open	3.5 × 1.5 × 7.1	37.4	Solid	Plum	White	Blue	No	No
Humira CD/UC Starter Package, 6 Pens 40 mg/0.8 mL NDC 0074-4339-06[a]	Yes	Top Open	6.1 × 2.1 × 7.9	100.9	Solid	Plum	White	Gold	No	No
Humira 2 Syringes Package 40 mg/0.8 mL NDC 0074-3799-02[a]	Yes	Top Open	3.3 × 2.2 × 6.5	48.0	Solid	Plum	Dark Gray	None	No	No
Humira Psoriasis (Ps) Starter Package, 4 Pens 40 mg/0.8 mL NDC 0074-4339-07[a]	Yes	Side Open	8.0 × 6.1 × 2.1	103.2	Solid	White	Lavender	Plum	No	No
Humira 2 Syringes Package 20 mg/0.4 mL Pediatric NDC 0074-9374-02[a]	Yes	Top Open	3.3 × 2.2 × 6.5	48.0	Solid	Gray	White	Plum	Yes	No
Humira 2 Syringes Package 10 mg/0.2 mL Pediatric NDC 0074-6347-02[b]	No	Side Open	6.5 × 3.3 × 2.2	53.3	Swoosh	White	Lavender	Plum	No	Yes
Humira Pediatric CD Starter Package, 3 Syringes 40 mg/0.8 mL 15 kg to < 40 kg NDC 0074-3799-03[b]	No	Side Open	7.2 × 7.6 × 2.1	115.5	Swoosh	Light Gray	White	Plum	Yes	Yes
Humira Pediatric CD Starter Package, 6 Syringes 40 mg/0.8 mL ≥ 40 kg NDC 0074-3799-06[b]	No	Side Open	7.1 × 10.6 × 2.1	159.2	Swoosh	Light Green	White	Plum	Yes	Yes

   c. Create a matrix that provides information regarding clinical impact on the user making packaging selection errors across the Humira product line.
      Summary of Response: The package selection matrix and clinical impact for all corresponding potential dispensing scenarios are provided in Appendix A of the response. The total errors observed in the human factors validation study were 4/117,

and one of these four resulted in a pharmacist releasing an incorrect dose equivalent of medication. The patient would have incorrectly received a 3-syringe Humira PCD Starter Package (3 Package (6 syringes, 40 mg/0.8 mL, ≥ 40kg) (Scenario 13). In this case, the patient would have received a lower than prescribed induction dose, which may have resulted in a longer time to reach a steady state serum concentration. The patient would have still received an induction dose; therefore, it would be expected that the patient would have still derived benefit, although it may have taken longer for the patient's symptoms to improve due to the delay in achieving steady state concentration. Such a scenario would not be expected to represent a risk to the patient.

d. Provide specific subjective data where pharmacy technicians responded to open-ended questions regarding their perspective and interpretation of why they failed to dispense the correct medication. Provide your analysis performed on those data determining whether they were caused by aspects of the proposed product user interface. Your indication that the participant rushing through the task or that the participant only focused on the dosage amount only was not helpful in our review.

e. Provide specific subjective data where the pharmacists responded to open-ended questions regarding their perspective and interpretation on why they failed to correct the errors seen with the pharmacy technicians, and provide your analysis performed on those data determining whether they were caused by aspects of the proposed product user interface.

   Summary of Response to d) and e): The analysis of the subjective data for the errors and instances where the technician selected the wrong package and the pharmacist corrected the error (i.e., close calls) for both the pharmacy technicians and the pharmacists is provided in Appendix B along with the clinical impact for the subjects who were dispensed a different dosage. The analysis revealed that the errors and close calls observed were not found to be directly related to the product packages or package designs, but due to other factors such as:

   - Matching dosage amount but not fully reading the prescription for other pertinent information,
   - Reliance on NDC codes to pick the correct product, which were not available in the human factors validation study
   - Not following up with the doctor when prescription information was incomplete, and
   - Unfamiliarity with the product and packaging.

f. Provide a rationale for why you believe you have optimized the product labeling to ensure safe and effective use.

   Summary of Response: There are a number of distinct differences across Humira packaging, including package size, colors, inverted font for dose, increased font size for dose on the side panel, artistic style, NDC codes, and package opening format (Table 1) that contribute to an optimized product label. In addition, specialty pharmacies have many verification checkpoints in place to ensure that the correct medication reaches the pharmacist and that the correct medication is dispensed to the patient. These checkpoints go beyond inspection of the package and product labeling and include comparison of NDC codes, matching bar codes and scanners, benefit verification documentation containing diagnosis, patient outreach including

verification with patient prior to dispensing, and, at some specialty pharmacies, an additional pharmacist to check the first pharmacist's work. Participants' unfamiliarity with the contents of the Starter Packages partially contributed to most of the errors in the human factors validation study. Therefore, it is important to communicate the introduction of the PCD Starter Packages in terms of what the packages look like, and the differences between them in terms of dosages of medication and patient weight. Such communication would be typical of a new product launch activity undertaken by AbbVie.

2. The Patients and Caregivers Validation Study Report showed 1 participant failed to complete all three tasks (initial dose, second dose, and maintenance dose), 2 participants failed to complete task 2, and 1 participant failed to complete task 3. We are concerned that these errors can result in sub-optimal treatment (i.e., underdose and overdose).
   a. Your analysis indicated that participants did not review the Starter Package Information and Calendar. If review of Starter Package Information and Calendar is required prior to use, you should communicate this requirement in your product labeling.
      Summary of Response: To further improve product labeling, AbbVie has included with this response proposed revisions to the Medication Guide and Instructions for Use to indicate that patients should review all materials that are provided with Humira before starting treatment (see Module 1.14.1.3). In addition, the first paragraph of the Instructions for Use was updated to include a statement that the patient should understand the dosing instructions prior to using Humira. These changes, in addition to the information already contained in the labeling, will instruct the patient and caregiver to read and follow the dosing instructions and will further optimize the patient instructions.
   b. In addition, provide specific subjective data where the patients and caregivers responded to open-ended questions regarding their perspective and interpretation on why they failed to perform to count the correct day using the Calendar.
      Summary of Response: The subjective data for the errors and close calls (i.e., instances where the participant made an error and self-corrected prior to the final answer) for both the patients and caregivers are provided in Appendix C. There were a total of 6 errors and 3 close calls in the patients/caregivers human factors validation study. The analysis revealed that the errors observed were not found to be directly related to the Starter Package labeling, but due to other factors, such as the user miscounting the days between doses, misreading the paper monthly calendar provided to keep track of calendar days, or rushing due to the test environment. While the errors reported during the human factors validation study could result in drug administration outside the dosing window, these deviations are not considered to adversely impact the effectiveness or safety profile of adalimumab.
   c. Provide a rationale for why you believe you have optimized the product labeling to ensure safe and effective use.
      Summary of Response: The dosing instructions for the PCD Starter Packages have been found to be safe and effective for the intended users, uses, and use environments as demonstrated in the patients/caregivers human factors validation study. The Starter Package contains an example calendar, which was tested during the human factors

validation study and contains dosing instructions to assist the patient with induction dosing. The human factors validation study found that the errors observed were not related to the actual Starter Package calendar or instructions but were due to the users miscounting the days between doses, misreading the paper monthly calendar provided to the user to keep track of calendar days, or rushing due to the test environment, rather than confusion over the Starter Package instructions as described in the subjective data. While the errors reported above would have resulted in dosing outside of the prescribed dosing frequency, these deviations would not be anticipated to adversely affect the effectiveness or safety profile of adalimumab.

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/s/

MATTHEW B BRANCAZIO
09/02/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance

DATE:	April 25, 2014
TO:	Matt Brancazio, CDER - DGIEP matthew.brancazio@fda.hhs.gov
Cc:	Office of combination products at combination@fda.gov
Through:	Francisco Vicenty, Chief, CDRH – DMQ – OC – REGO

Francisco Vicenty -S
2014.05.01 19:58:23 -04'00'

From:	Viky Verna, MS BME, MS Pharm, Reviewer, CDRH – DMQ – OC – REGO, WO66, Room 2628
Firm:	AbbVie, Incorporated 1 North Waukegan Road North Chicago, Illinois 60064
Application #	BLA 125057/356
Product Name:	Humira® (adalimumab)
Consult Instructions:	Review documents provided by the applicant to evaluate compliance with Quality System Regulations and to determine the need for inspection.

Background
The Office of Compliance at CDRH received a consult request from Matt Brancazio, CDER, to review the documents provided by the applicant to evaluate its compliance with Quality System Regulations and to determine the need for inspection.

Combination Product Description
HUMIRA is a prescription medicine used alone, with methotrexate, or with certain other medicines to reduce the signs and symptoms of moderate to severe rheumatoid arthritis in adults.

This supplement is intended to support an indication for use in pediatric patients aged 6 years and older with moderately to severely active Crohn's disease and also to register a 10 mg/0.2 mL, pre-filled syringe presentation for the purpose.

The formulation and container closure of the drug product in the 10 mg/0.2mL PFS presentation is identical to the approved Humira presentations.

Review

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. A description of the manufacturing process for the 10 mg PFS was submitted, as well as validation, batch release, and stability data. The description and composition, batch formula, and specifications were also submitted for the 10 mg PFS.

The firm explained that the qualitative and quantitative composition of the 50 mg/mL adalimumab bulk drug product solution used in the manufacture of the 10 mg/0.2 mL pre-filled syringe (PFS) is identical to that used for production of the approved 40 mg/0.8 mL and 20 mg/0.4 mL pre-filled syringes. The manufacturing process and in-process controls also remain the same up to the point of filling the syringes. The only difference is the volume of solution filled into the syringe (0.2 mL versus 0.8 mL or 0.4 mL). The only changes to the filling process is a (b) (4) (b) (4). The stopper placement equipment is set to maintain a comparable headspace between the solution and the stopper for all 3 PFS fill volumes (i.e., for the approved nominal 0.8 mL and nominal 0.4 mL fill volumes for the 40 mg and 20 mg PFS, respectively, as well as for the proposed nominal 0.2 mL fill volume for the 10 mg PFS).

The container-closure system for the primary packaging of the adalimumab solution for injection, 50 mg/mL, 10 mg/0.2 mL PFS uses the approved packaging systems for the current Humira drug products, i.e. (b) (4) syringe system. The system utilizes syringes staked with a 27 G needle and uses a natural rubber needle shield and a (b) (4) rubber plunger stopper.

All three presentations are manufactured at the (b) (4) site in (b) (4) The manufacturing of the adalimumab 50 mg/mL solution for injection, 10 mg/0.2 mL PFS in (b) (4) was validated at the (b) (4) (b) (4) (b) (4). For the validation, all steps in the production process were controlled within ranges specified in the manufacturing directions. The container closure integrity for (b) (4) batches was assessed and met all acceptance criteria. The process validation demonstrated that the manufacturing process can consistently generate acceptable final product of 10 mg/0.2 mL PFS at (b) (4) site either by the (b) (4) or (b) (4) process.

To ensure the current shipping method for the Humira 40 mg/0.8 mL PFS does not impact the container integrity of the 10 mg/0.2 mL PFS, shipping studies were also performed on the (b) (4) batches of 10 mg/0.2 mL PFS. All syringes met the acceptance criteria of the container closure integrity testing procedure. These results demonstrate that the shipping method in place for the currently approved Humira PFS is also appropriate for the 10 mg PFS.

Deficiencies

1. The firm provided a table with the functions of the different manufacturers involved in the manufacturing of the Adalimumab, single dose syringe, 10 mg/0.2 mL. However, the sponsor firm did not provide documents covering the agreement it has with its contract manufacturers listing the parties' responsibilities. The firm did not provide documents for purchasing controls or incoming inspection activities to be performed at the sites responsible for final release of the combination products. There were no documents covering the purchasing controls over the syringes to be used. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.50.

Firm's Response Review

The firm's response dated February 28, 2014, is adequate. In its response the firm provided information confirming it has established Quality Agreements per SD.18.07.01 *Quality Assurance Supplier Evaluation, Monitoring, and Approval* and QSD.18.07.02 *Global Finished Goods Third Party Management Process* for contract manufactures and service providers involved in the supply of product to the US market. The quality agreement established with (b) (4) will be updated to include specific references for the 10 mg/0.2 mL single dose syringe as part of the product listing once the first market approval is gained.

The aforementioned procedures also govern the AbbVie process for Purchasing Controls and the supply acceptance activities and conformance to specification are assured by QSD.17.03.01 *Material Control/Disposition.* These AbbVie procedures define the controls for materials and services purchased and/or received directly by AbbVie. For materials and services purchased and/or received directly by (b) (4) as part of the contracted manufacturing process for the 10 mg/0.2 mL single dose syringe, including the empty syringes to be used for the 10 mg/0.2 mL prefilled syringes, the quality agreement identified above outlines the responsibilities for purchasing and material controls to be established at (b) (4). The activities conducted at (b) (4) according to the referenced agreement are monitored as part of AbbVie's periodic compliance audit program for suppliers and contract manufacturers.

QSD.17.03.01 *Material Control/Disposition* describes the quality system governing the control and inspection of materials received by AbbVie for release into the US market. This includes the inspection and control of bulk, unlabeled, pre-filled adalimumab syringes manufactured by (b) (4) and shipped to the AbbVie in North Chicago, IL USA for final packaging, labeling and batch release as well as pre-filled syringes that may be final packaged and labeled for the US market by (b) (4) prior to delivery to AbbVie. In the case of pre-filled syringes labeled and packaged by (b) (4), the inspection and control of the pre-filled syringes is conducted by AbbVie Deutschland GmbH & Co. KG with final batch release by AbbVie Biotechnology GmbH.

REGULATORY HISTORY

(b) (4)

Function: PFS Drug Product manufacturing including visual inspection of bulk PFS, batch release and stability testing for sterility and bacterial endotoxin for the bulk PFS

A Level II device inspection, conducted on 12/02-05/2013, was classified as VAI. The previous inspection of the firm was conducted on 10/29/12-11/09/12 and resulted in the issuance of a 19 item form FDA 483 (OAI).

- AbbVie, Incorporated
1 North Waukegan Road
North Chicago, Illinois 60064
FEI: 3009751352
Function: Labeling and packaging of pre-filled syringe patient and hospital use presentations and pre-filled pen presentation. Batch release of finished pre-filled syringes labeled and packaged at Abbott Park

The first medical device inspection of the site which was performed on 12/03-13/2013, and pertained to BLA 125057/353 supplement for the Humira Autoinjector pens. The inspection resulted in a three observation FDA 483 (VAI).

The last inspection at this firm, a FY'13 Abbreviated Drug cGMP inspection, was performed on 09/04/2013 and was classified as NAI. The previous inspection of the firm was on 4/22-25/13 and was a pre-approval and cGMP inspection and was classified as NAI. It was the first inspection of AbbVie Inc.

- AbbVie Biotechnology GmbH
Max-Planck-Ring 2
D-65205 Wiesbaden, Germany
FEI: 3002809144
Function: Batch release of bulk pre-filled syringes for labeling and packaging. Batch release of finished prefilled syringes if labeled and packaged at (b) (4)

The last two inspections at the firm were classified as NAI. This facility received an in vitro diagnostic Class III test kit device inspection 6/10/2013 - 6/13/2013 and a QSIT Level II inspection 9/20/2010 - 9/23/2010.

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of the supplement BLA 125057/356. There were no deficiencies found with the supplement. Therefore the Office of Compliance at CDRH is recommending approval of the supplement.

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2014.05.05 09:02:00 -04'00'

Viky G. D. Verna, MS BME, MS Pharm

Prepared: VVerna: April 25, 2014
Revised: FVicenty: May 1, 2014

cc:

WO66-2628 Viky Verna

WO66-2628 Carl Fischer

WO22-5345 Matt Brancazio

combination@fda.gov (OCP)

BLA 125057/356

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/s/

MATTHEW B BRANCAZIO
08/19/2014
Administratively entered for CDRH reviewer.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 15, 2014

To: Matthew Brancazio, Pharm.D.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: sBLA 125057/356
OPDP Comments for draft Humira (adalimumab) injection, for subcutaneous use PI and Medication Guide

OPDP has reviewed the proposed draft PI for Humira. We have reviewed the draft PI and Medication Guide, retrieved from Sharepoint on August 15, 2014, and have the following comments.

Thank you for the opportunity to comment on the proposed PI and Medication Guide.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/15/2014

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:	August 14, 2014
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)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	HUMIRA (adalimumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 125057
Supplement Number:	356
Applicant:	AbbVie Inc.

1 INTRODUCTION

On August 29, 2013, AbbVie, Inc. submitted for the Agency's review a Prior Approval Supplement to their Biologics Licensing Application (BLA) 125057/356 for HUMIRA (adalimumab). This efficacy supplement provides for updates to the HUMIRA Prescribing Information (PI) for the proposed new indication for reducing the signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who (b) (4)

HUMIRA (adalimumab) was originally approved on December 31, 2002 and 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
- Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 4 years of age and older
- Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis
- Reducing signs and symptoms in adult patients with active ankylosing spondylitis
- 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
- 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)
- 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

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on August 5, 2014, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for HUMIRA (adalimumab) injection.

2 MATERIAL REVIEWED

- Draft HUMIRA (adalimumab) injection MG received on August 29, 2013 and received by DMPP on August 5, 2014.

- Draft HUMIRA (adalimumab) injection IFU received on August 29, 2013 and received by DMPP on August 5, 2014.
- Draft HUMIRA (adalimumab) injection Prescribing Information (PI) received on August 29, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on August 5, 2014.

3 REVIEW METHODS

In our focused review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG and IFU are 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 or IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
08/14/2014

BARBARA A FULLER
08/14/2014

LASHAWN M GRIFFITHS
08/14/2014

LABEL AND LABELING AND HUMAN FACTORS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 16, 2014
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type, Number, and Supplement:	BLA 125057/S-356
Product Name and Strength:	Humira (Adalimumab) Injection 40 mg/0.8 mL prefilled pen, prefilled syringe, & vial 20 mg/0.4 mL prefilled syringe
Product Type:	Combination (drug + device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie, Inc.
Submission Date:	August 29, 2013
OSE RCM #:	2013-2163, 2013-2164
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Associate Director:	Lubna Merchant, PharmD, MS

1 REASON FOR REVIEW

This review responds to a request from DGEIP to evaluate the applicant's Human Factor Validation Study Results as well as the container label, carton labeling, and Prescribing Information, associated with Humira (Adalimumab), to ensure the intended population is able to use the product safely and effectively.
AbbVie, Inc. submitted an efficacy supplement for Humira to expand the Crohn's Disease indication to include patients 6 years of age and older.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed. In addition, a FDA Adverse Event Reporting System (FAERS) 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, #2010-2102 and #2009-935.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B- (N/A)
Previous DMEPA Reviews	C-(N/A)
Human Factors Study	D
ISMP Newsletters	E-(N/A)
Other	F-(N/A)
Container Label, Carton Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 Dosing Comprehension for Humira Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report

The applicant is proposing a pediatric Crohn's Disease indication for patients six years and older. Overall, the dosing comprehension study results demonstrated that participants were able to comprehend the dosing instructions for the proposed pediatric Crohn's Disease indication appropriately. However, there were some errors and close calls which were attributed to participants miscounting the days in between doses, misreading the calendar, and rushing due to the test environment. We note that these errors may result in a patient receiving a dose outside of the dosing window. The applicant states that these deviations should not adversely impact the safety profile of this product. We defer to DPARP to determine if these deviations adversely impact the effectiveness or safety profile of this product. We also reviewed the dosing calendar to see if it could be further optimized to help mitigate the errors and close calls noted. We find the calendar uses multiple ways (e.g. circling/highlighting the day of dose and including a picture of the number of syringes on day of dose) to help patients identify the day and dose. We find the dosing calendar acceptable. We also note that none of the participants were trained and in a real-world scenario a healthcare provider would explain the dosing schedule. In addition, the applicant has proposed to include instructions in the Medication Guide and Instructions for Use for all users to review all materials prior to starting treatment and that all users should understand the dosing instructions prior to using this product.

3.2 Humira Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report

Overall, the human factors study results demonstrated that the carton labeling for the Humira product line is adequately differentiated to minimize selection errors. However, some errors and close calls occurred (participants not correctly calculating the dose, focused on dispensing the correct dose and number of pens or syringes, not contacting the physician when having an incomplete script, and not familiar with the product packaging). We note that these errors and close calls may result in wrong dose errors. However, multiple verification checkpoints (e.g. training, bar code scanning, comparison of NDC codes, other quality assurance practices such as procedural checks in place to ensure accurate prescription dispensing processes) that may help mitigate these errors and close calls were not implemented for this human factors study and we also note that the pediatric starter packages will only be dispensed in a specialty pharmacy which should include these verification checkpoints.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors Studies demonstrated that users are able to comprehend the pediatric Crohn's dose and the carton labeling for the Humira line is adequately differentiated. However, some users of this product and persons involved in dispensing this product may encounter difficulties. Training all users and implementing verification checkpoints for those dispensing this product should help mitigate the errors and close calls identified in the study.

4.1 RECOMMENDATIONS FOR THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Carton Labeling [Trade/Professional Sample]

1. Ensure that the image of the prefilled syringe accurately represents the, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength. [3]

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Humira (Adalimumab) that AbbVie submitted on August 29, 2013.

Table 2. Relevant Product Information for Humira (Adalimumab)	
Active Ingredient	Adalimumab
Indication	Treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Crohn's Disease, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis, and Ulcerative Colitis
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL, 40 mg/0.8 mL
Dose and Frequency	(b) (4) mg, 20 mg, 40 mg, 80 mg, or 160 mg every other week
How Supplied	Single-use Prefilled syringe, Single-use Pen
Storage	Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F) and should be protected from exposure to light.
Proposed Additions to the Humira (Adalimumab) product line	10 mg/0.2 mL-Prefilled syringe 40 mg/0.8 mL Pediatric Crohn's Disease Starter Kits for >40 kg and <40 kg

APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

D.1.1 Dosing Comprehension for Humira Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report

The objective of this study was to evaluate if participants could comprehend the dosing instructions.

There were a total of 22 participants which consisted of parents, caregivers, and adolescents (age 15-17).

The participant demographics included:

- 17 Adults, 5 Adolescents
- 6 Males, 16 Females
- Average Age of participant was 3 years old. Ages ranged from 15-57 years.

Three critical tasks were tested:

• Task 1: Each participant was asked to mark dose 1 as "today's" date on the monthly calendar they were given. When ready to "inject", they pulled an empty syringe dose tray from the Starter Package and handed it to the moderator to simulate administering a dose of medicine to their child or him/herself. This process was repeated until participants stated that they had administered all the medicine for Dose 1.

• Task 2: After completing Task 1, the moderator asked the participant to mark the date when they would administer the next dose of medication (dose 2) to their child or him/herself on the paper calendar provided.

***Participants were then instructed to store the medication in the refrigerator as this is where it would be kept in real life. After some time had passed, the moderator announced that it was now the day that the participant had marked on their calendar

and asked the participant to retrieve the stored medication and continue administering medication to their child or him/herself in the same process described above in Task 1.

- Task 3: Upon completion of Task 2, participants were asked to mark the paper calendar with the date when he or she would administer the next dose of medication to their child or him/herself (Maintenance Dose).

Participants were not trained prior to initiation of the study.

D.1.2 Humira Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report

This human factors validation study had the following objectives:

- Assess the ability of specialty pharmacists and pharmacy technicians to successfully fill prescriptions without selection error across a range of packages including the packages introduced with the Humira Pediatric Crohn's Disease indication (two new starter packages and a 10 mg 2 pre-filled syringe package) and other commercially available Humira packages.
- Assess whether there are sufficient differences between the new package designs introduced with the new packages introduced with Pediatric Crohn's Disease (PCD) (two Starter Packages and a 10 mg 2 pre-filled syringe package) and current commercially available Humira package designs to ensure accurate product identification and selection in a specialty pharmacy setting.

There were a total of 30 participants which consisted of 15 pharmacy technicians and 15 pharmacists. They were given four types of prescriptions which included the following: specialty pharmacy intake forms, handwritten, telephone, and handwritten with missing information.

D.2 Results

D.2.1 Dosing Comprehension for Humira Patients and Caregivers of Patients with Pediatric Crohn's Disease Validation Study Report

Task	N	# Success	# Fail	# Close Call
Task 1: Initial Dose	22	20	1	1
Task 2: Dose 2	22	18	3	1

Task	N	# Success	# Fail	# Close Call
Task 3: Maintenance Dose	22	19	2	1

D.2.2 Humira Pharmacist and Pharmacy Technician Human Factors Summative Validation Research Study Report

	N	# Success	# Fail	# Close Call
By Participant Pair	15	6	3	6
By Overall Trial	117[3]	96	4	17

Across all trials counted, there were 4 failures and 17 close calls. Of the four failures, 3 had no risk to the patient because the orders were filled with a dose equivalent to that on the prescription. All of the close calls were returned to the technician to be refilled and therefore had no risk to the patient.

The seven pharmacists who attempted the prescription filling task succeeded by correctly filling the order given to them over the phone.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following adalimumab labels and labeling submitted by AbbVie on August 29, 2013.

- Trade/Professional Sample Container label
- Trade/Professional Sample Carton labeling

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
05/16/2014

LUBNA A MERCHANT
05/16/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From:	Ethan D. Hausman, MD, Medical Officer Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND)
Through:	Hari Cheryl Sachs, MD, Team Leader, PMHS, OND Lynne P. Yao, MD OND Associate Director PMHS, OND
BLA Number:	125057
Sponsor:	Abbvie, Inc.
Drug:	Humira (adalimumab)
Dosage form and route of administration:	Subcutaneous (SC)
Proposed Indication:	For the treatment of pediatric Crohn's disease (PCD)
Consult request:	The Division of Gastroenterology and Inborn Error Products (DGIEP) requests input from PMHS to appropriately label this product.

Background

FDA approved Humira (adalimumab) for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS) on December 31, 2002. Adalimumab was subsequently approved for the following indications in adults: treatment ankylosing spondylitis (September 2006), psoriatic arthritis (November, 2006), Crohn's disease (February, 2007), plaque psoriasis (January, 2008), and ulcerative colitis (September 2012). The only approved pediatric indication to date is for the treatment of juvenile idiopathic arthritis (JIA, February, 2008).

The Approval Letter in February 2007 for the indication for treatment of adults with Crohn's disease in adults required the following deferred pediatric study under provisions of the Pediatric Research Equity Act (PREA):

> "To complete and submit data from study protocol M06-806, a one-year, multi-center, randomized, double-blind study designed to evaluate the safety, efficacy, and pharmacokinetics of adalimumab in the induction and maintenance of clinical remission in pediatric subjects 6 to 17 years of age with moderate to severe Crohn's disease. The study will include collection of baseline data on prior loss of response to or intolerance to infliximab, using definitions similar to those used in protocol M04-69l. The final study protocol was submitted to Abbott's IND on January 24, 2007. Enrollment of 186 patients will begin by March 31, .2007, and will be complete by March 31, 2008."

The above study was to be completed by March 31, 2009, and the final clinical study report was to be submitted by December 31, 2009. The indication for pediatric Crohn's disease (PCD) received orphan designation on October 19, 2006.

Reviewer comment: The drug received orphan designation for pediatric Crohn's disease (October 2006) after the application for that indication was received; therefore the agency determined that PREA applies, even though orphan designation was granted prior to approval.

The sponsor submitted two studies in order to meet the PREA requirement. On August 29, 2013, the sponsor submitted two complete study reports (Studies M06-806 and M06-807) to support an indication for treatment of children with Crohn's disease ages 6 through 17 years.

Reviewer comment: Studies M06-806 (induction remission and short term safety) and M06-807 (long term safety and maintenance of remission) have previously been reviewed. The reader is referred to the reviews by DGIEP, Clinical Pharmacology, Statistics, and other FDA disciplines for comprehensive analyses of the studies.

Discussion

The development plan for treatment of pediatric Crohn's disease in children 6 years and older employs partial extrapolation (i.e., similarity of disease and expected response to treatment) and a single adequate and well-controlled trial for the pediatric indication might be sufficient to support safety and efficacy. The reader is directed to the primary reviews for an assessment of the adequacy of the data.

The label has been reviewed in its entirety; however, the PMHS pediatric labeling review is restricted to the newly proposed language in section 8.4 for Pediatric Crohn's disease. The language proposed by the sponsor is presented first, followed by suggested revisions from PMHS (***in italicized and bold type***).

Language Proposed by the Sponsor

Pediatric Crohn's Disease

(b) (4)

PMHS-Pediatric Team Labeling Recommendations

8.4 Pediatric Use

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

Pediatric Crohn's Disease

(b) (4)

Conclusion and Recommendations

The above comments were provided to DGIEP in advance of internal labeling meetings and should be addressed during labeling discussions. PMHS will continue to participate in labeling discussions. The reader is directed to final labeling which will be available upon approval.

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/s/

ETHAN D HAUSMAN
08/06/2014

HARI C SACHS
08/06/2014
I agree with these recommendations.

LYNNE P YAO
08/11/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: March 25, 2014

From: Miriam Dinatale, D.O., Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: OND/ODEIII/DGIEP

Drug: Humira (adalimumab) Injection, Solution for Subcutaneous Use

BLA: 125057

Applicant: AbbVie Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed: Proposed Humira product labeling, PMHS Humira memo 3/13/13

Consult Question:
"PMHS to review and comment on the labeling for this efficacy supplement"

INTRODUCTION

On August 29, 2013, AbbVie, Inc. submitted an efficacy supplement for Humira, BLA 125057, to expand the Crohn's Disease indication to include patients 6 years of age and older.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff- Maternal Health Team (PMHS-MHT) on October 23, 2013, to provide input for appropriate labeling of the pregnancy and nursing mothers' subsections of Humira labeling.

BACKGROUND

Humira (adalimumab), initially approved in the U.S. on December 31, 2002, is a recombinant human immunoglobulin (IgG1) monoclonal antibody specific for human tumor necrosis factor (TNF). Humira is approved for the treatment of Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Crohn's Disease (CD), Ulcerative Colitis (UC), and Plaque Psoriasis. Humira has been associated with serious adverse reactions including infections, such as tuberculosis, bacterial sepsis and invasive fungal infections and malignancy, such as lymphoma and non-melanoma skin cancer, which are included in a boxed warning on the current label.

Humira received a Pregnancy Category B classification based on negative reproductive studies conducted in cynomolgus monkeys and no human data at the time of initial approval. As previously stated, adalimumab is an IgG1monoclonal antibody. IgG1 class antibodies are actively transferred across the placenta during the third trimester of pregnancy. Generally, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. On March 13, 2013[1], PMHS-MHT recommended pregnancy and nursing mothers labeling revisions for a Humira prior approval labeling supplement that had been submitted on August 10, 2012, to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), to provide for the addition of published placental transfer data in subsection 8.1 Pregnancy and additional guidance for breastfeeding in subsection 8.3 Nursing Mothers. PMHS-MHT labeling recommendations were accepted by the applicant and Humira pregnancy and nursing mothers labeling was updated on May 13, 2013. Additionally, Humira pregnancy exposure data are currently being collected by The Organization of Teratology Experts (OTIS) Autoimmune Diseases in Pregnancy Project.[2]

Women with inflammatory bowel disease (IBD) have higher risks of pregnancy complications, such as spontaneous abortion, preterm birth, and complications of labor and delivery compared with the age-matched general population, even when their disease is inactive. Active disease is associated with a further increase in preterm birth and miscarriage. Stopping effective medications for IBD can lead to a high risk of flare within a

[1] Maternal Health Team Review on Pregnancy and Lactation Labeling for Humira (adalimumab): BLA 125057, 3/13/2013.

[2] A study to gain additional information regarding autoimmune diseases, their treatment during pregnancy, and the potential effects of the treatment on the developing embryo or fetus.

year. Most IBD clinical practice guidelines recommend continuing maternal drug therapy during pregnancy.[3]

Current Approved Humira Pregnancy and Nursing Mothers Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with HUMIRA have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Adalimumab serum levels were obtained from ten women treated with HUMIRA during pregnancy and eight newborn infants suggest active placental transfer of adalimumab. No fetal harm was observed in reproductive studies performed in cynomolgus monkeys. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Human Data

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal blood as well as in cord (n=10) and infant blood (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant blood, and 0-16.1 µg/mL in maternal blood. In all but one case, the cord blood level of adalimumab was higher than the maternal level, suggesting adalimumab actively crosses the placenta. In addition, one infant had levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed in utero for at least 3 months from birth.

Animal Data

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.

[3] Mahadevan, Uma. "Placental Transfer of Anti-Tumor Necrosis Factor Agents in Pregnant Patients with Inflammatory Bowel Disease." Clinical Gastroenterology and Hepatology. 2013. 11; 286-292

8.3 Nursing Mothers
Limited data from published literature indicate that adalimumab is present in low levels in human milk and is not likely to be absorbed by a breastfed infant. However, no data is available on the absorption of adalimumab from breastmilk in newborn or preterm infants. Caution should be exercised when HUMIRA is administered to a nursing woman.

DISCUSSION
PREGNANCY AND NURSING MOTHERS LABELING
The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

CONCLUSIONS
The Pregnancy and Nursing Mothers subsections of Humira labeling were updated May 13, 2013, and no revisions are necessary at this time. The current approved Humira labeling adequately reflects appropriate pregnancy and lactation information for clinical decision making and management of pregnant and lactating women who may require treatment with the product.

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