CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125057/46

Trade Name: Humira®

Generic Name: adalimumab

Sponsor: Abbott Laboratories

Approval Date: 10/03/2005

Indication: Request to supplement biologics license application for adalimumab to expand indication to include recently diagnosed patients with moderately to severely active rheumatoid arthritis who have not received Methotrexate.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125057/46

OCT 03 2005

Abbott Laboratories
Attention: James D. Steck, R.Ph.
Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL, 60064-6157

Dear Mr. Steck:

Your request to supplement your biologics license application for adalimumab to expand the indication to include recently diagnosed patients with moderately to severely active rheumatoid arthritis who have not received Methotrexate has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge your plan to evaluate the feasibility of conducting a study in patients aged 0 to less than 4 years, and if appropriate, submit a pediatric study plan or request a waiver by March 31, 2007. Therefore, we are deferring submission of your pediatric studies for ages 0 to 4 years until this date.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)

Summary Text: Clinical Supplmt. Efficacy - Expanded Indication
LETTER: Pediatric Partial Deferral (PPD)

REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).

RIS Data Check:

- Verify short summary - Ltr. & Submission screen should match.
- Check Letter for PMCs (if PMCs - add "PMCs - Approved With" special characteristic code.)
- Check if Major Approval - if so - add code.
- Perform Review Completion Process
- Milestone: Confirm Approved Status

cc: Attached label is sent to everyone
HFD-108/M. Walton
HFD-108/J. Siegel
HFD-108/A. Gorovets
HFD-109/E. Laughner
HFD-108/K. Scheider
HFD-711/K-Y. Lee
HFD-711/B. Zhen
HFD-711/A. Chakravarty
HFD-430/H. Kwon
HFD-107/L. Martynec
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HFD-006/Exec sec P. Guinn
HFD-013/FOI H. Brubaker
HFD-240/OTCOM/ B. Poole
HFI-20/Press/ L. Gelb
HFI-20/Press/ J. Brodsky

HFD-230/OTCOM/CDER WebMaster
HFD-109/C. O'Leary
HFD-42/DDMAC/M. Kiester
HFD-410/ODS/DSRCS/ Karen Young
CDER-OCTAP960PM (PEDs e-mail account)
HFD-322/IPCB/ E. Rivera-Martinez
HFM-555/DMA/ S. Kozlowski
HFM-535/DTP/ A. Rosenberg
HFD-328/TFRB Blue File/Mike Smedley
HFD-430/ODS/DDRE (hard copy)
HFD-410/CDER Medwatch Safety Labeling (hard copy)
DRMP BLA file (hard copy)

History: E. Laughner: 09/27/05; 09/30/05

File Name:
(S:\Laughner\BLA\125057\125057 46\125057 46AP.doc)

Office	Name/Signature	Date
DRMP	E. L	10-3-05
DRMP	Schneider	10-3-05
OTBEMP		10/3/05
ODE/DBOP		10/28/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

LABELING

(No. 3799)
NEW

HUMIRA®
(adalimumab)

Rx only
Tear at Perforation to Dispense Patient Information

WARNING

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING HUMIRA. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH LATENT TUBERCULOSIS INFECTION REDUCES THE RISK OF REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH HUMIRA. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING HUMIRA WHOSE SCREENING FOR LATENT TUBERCULOSIS INFECTION WAS NEGATIVE.

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING HUMIRA FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

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:κ constant regions. HUMIRA 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 in single-use, 1 mL pre-filled glass syringes as a sterile, preservative-free solution for subcutaneous administration. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH.

CLINICAL PHARMACOLOGY

General

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 rheumatoid arthritis and psoriatic arthritis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.

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).

Pharmacodynamics

After treatment with HUMIRA, a rapid 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. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after HUMIRA administration.

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 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- 96% of those in serum.

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. The 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.

Population pharmacokinetic analyses 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 patients receiving doses lower than the recommended dose and in 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.

HUMIRA has not been studied in children.

Drug Interactions

MTX reduced adalimumab apparent clearance after single and multiple dosing by 29% and 44% respectively.

CLINICAL STUDIES

Rheumatoid Arthritis

The efficacy and safety of HUMIRA were assessed in five randomized, double-blind studies in patients ≥ age 18 with active rheumatoid arthritis 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 MTX (12.5 to 25 mg, Studies I, III and V) or as monotherapy (Studies II and V) or with other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV).

Study 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 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 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 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 104 weeks.

Study 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 V evaluated 799 patients with moderately to severely active rheumatoid arthritis 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 II and III are shown in Table 1.

Table 1: ACR Responses in Studies II and III (Percent of Patients)

	Study II Monotherapy (26 weeks)			Study III Methotrexate Combination (24 and 52 weeks)	
Response	Placebo N=110	HUMIRA 40 mg every other week N=113	HUMIRA 40 mg weekly N=103	Placebo/MTX N=200	HUMIRA/MTX 40 mg every other week 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 I were similar to Study III; patients receiving HUMIRA 40 mg every other week in Study 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 II and III are shown in Table 2. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study 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.

Table 2: Components of ACR Response in Studies II and III

Parameter (median)	Study II				Study III			
	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

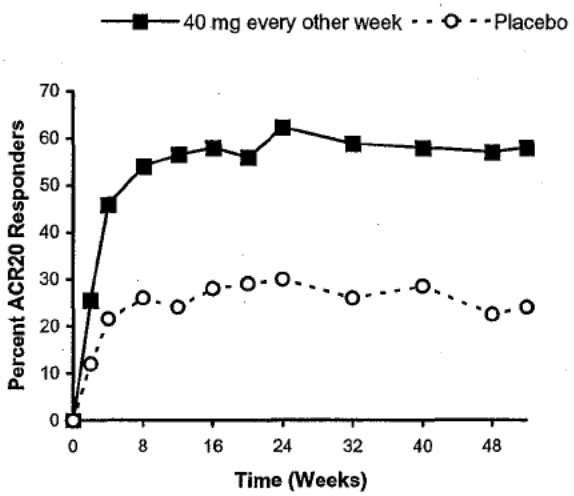
[c] Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

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

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

In Study 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 I and Study II were similar.

Figure 1: Study III ACR 20 Responses over 52 Weeks



In Study 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 V with MTX naïve patients with recent onset rheumatoid arthritis, 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 3).

Table 3: ACR Response in Study 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 V improved in the HUMIRA/MTX group and improvements were maintained to Week 104.

Radiographic Response

In Study 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 4. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

Table 4: Radiographic Mean Changes Over 12 Months in Study 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 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.

In Study V, structural joint damage was assessed as in Study 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 5).

Table 5: Radiographic Mean Change* in Study 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 I-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 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. Eighty-two percent of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study maintained that improvement through week 104 of open-label treatment. Improvement in SF-36 was also maintained through week 104.

In Study 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.

Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. Study PsA-I enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>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 psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-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 6 and 7). Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks). 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 6: ACR Response in PsA I (Percent of Patients)

Response	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 7: Components of Disease Activity in 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.

INDICATIONS AND USAGE

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 MTX or other DMARDs.

HUMIRA is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

CONTRAINDICATIONS

HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS

SERIOUS INFECTIONS

SERIOUS INFECTIONS, SEPSIS, TUBERCULOSIS AND RARE CASES OF OPPORTUNISTIC INFECTIONS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF HUMIRA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREDISPOSE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS- Tuberculosis and ADVERSE REACTIONS- Infections). THE

BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended (see PRECAUTIONS, Drug Interactions).

Neurologic Events

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 demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active RA, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.4, 1.3)/100 patient-years among 1922 HUMIRA-treated patients versus a rate of 0.4 (0.1, 1.2)/100 patient-years among 947 control patients (median duration of treatment of 5.6 months for HUMIRA-treated patients and 5.2 months for control-treated patients). The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. In the controlled and uncontrolled open-label portions of the clinical trials of HUMIRA, the more frequently observed malignancies, other than lymphoma and non-melanoma skin cancer, were breast, colon, prostate, lung and uterine. These malignancies in HUMIRA-treated and control-treated patients were similar in type and number to what would be expected in the general population.[6] During the controlled portions of HUMIRA rheumatoid arthritis trials, the rate (95% confidence interval) of non-melanoma skin cancers was 0.9 (0.56, 1.55)/100 patient-years among HUMIRA-treated patients and 0.3 (0.07, 1.07)/100 patient-years

among control patients. The potential role of TNF blocking therapy in the development of malignancies is not known.[4,5]

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled trials in patients with rheumatoid arthritis, 2 lymphomas were observed among 1922 HUMIRA-treated patients versus 1 among 947 control patients. In combining the controlled and uncontrolled open-label portions of these clinical trials with a median duration of approximately 3 years, including 3042 patients and over 8500 patient-years of therapy, the observed rate of lymphomas is approximately 0.15/100 patient-years. This is approximately 4-fold higher than expected in the general population.[6] Rates in clinical trials for HUMIRA cannot be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Hypersensitivity Reactions

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

Hematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA (see **ADVERSE REACTIONS, Other Adverse Reactions**). The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised 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. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

Information to Patients

The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see **HUMIRA, PATIENT INFORMATION LEAFLET**). A puncture-resistant container for disposal of needles and syringes should be used. Patients or caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

Tuberculosis

As observed with other TNF blocking agents, tuberculosis associated with the administration of HUMIRA in clinical trials has been reported (see **WARNINGS**). While cases were observed at all doses, the incidence of tuberculosis reactivations was particularly increased at doses of HUMIRA that were higher than the recommended dose.

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis infection with a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines[7] should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Patients with 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 events was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Immunosuppression

The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and

modulates cellular immune responses. In a study of 64 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils. The impact of treatment with HUMIRA on the development and course of malignancies, as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**). The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations

No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

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, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

Methotrexate

HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see **CLINICAL PHARMACOLOGY: Drug Interactions**). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra with other TNF-blocking agents, including HUMIRA, may also result in similar toxicities (see **WARNINGS, SERIOUS INFECTIONS**).

Carcinogenesis, Mutagenesis, and 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.

Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of HUMIRA in pediatric patients have not been established.

Geriatric Use

A total of 519 patients 65 years of age and older, including 107 patients 75 years and older, received HUMIRA in clinical studies. No overall difference in effectiveness was observed between these subjects and younger subjects. The frequency of serious infection and malignancy among HUMIRA treated subjects over age 65 was higher than for those

under age 65. Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

General

The most serious adverse reactions were (see **WARNINGS**):

- Serious Infections
- Neurologic Events
- Malignancies

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 events during the double-blind, placebo-controlled portion of Studies I, II, III and IV was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse events leading to discontinuation of HUMIRA were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

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.

Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see **WARNINGS**).

In completed and ongoing global clinical studies that include over 13000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of miliary, lymphatic, peritoneal, as well as pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal (see **WARNINGS**). In postmarketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials (see **WARNINGS**).

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.

Immunogenicity

Patients in Studies I, II, and 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 rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events 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.

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. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including 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

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 I, II, III, and 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 8 summarizes events 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. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 8: Adverse Events Reported by ≥ 5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

	HUMIRA 40 mg subcutaneous Every Other Week (N=705)	Placebo (N=690)
Adverse Event (Preferred Term)	Percentage	Percentage
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		
Injection site pain	12	12
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

608 * Laboratory test abnormalities were reported as adverse events in European trials
609 ** Does not include erythema and/or itching, hemorrhage, pain or swelling
610
611 ## Other Adverse Events

612 Other infrequent serious adverse events occurring at an incidence of less than 5% in
613 rheumatoid arthritis patients treated with HUMIRA were:
614
615 **Body As A Whole:** Fever, infection, pain in extremity, pelvic pain, sepsis, surgery,
616 thorax pain, tuberculosis reactivated
617
618 **Cardiovascular System:** Arrhythmia, atrial fibrillation, cardiovascular disorder, chest
619 pain, congestive heart failure, coronary artery disorder, heart arrest, hypertensive
620 encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis,
621 syncope, tachycardia, vascular disorder
622
623 **Collagen Disorder:** Lupus erythematosus syndrome
624

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

Endocrine System: Parathyroid disorder

Hemic And Lymphatic System: Agranulocytosis, granulocytopenia, leukopenia, lymphoma like reaction, pancytopenia, polycythemia (see **WARNINGS, Hematologic Events**).

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, carcinomas such as breast, gastrointestinal, skin, urogenital, and others; lymphoma and melanoma.

Nervous System: Confusion, multiple sclerosis, paresthesia, subdural hematoma, tremor

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

Skin And Appendages: Cellulitis, erysipelas, herpes zoster

Special Senses: Cataract

Thrombosis: Thrombosis leg

Urogenital System: Cystitis, kidney calculus, menstrual disorder, pyelonephritis

HUMIRA has been studied in 395 patients with psoriatic arthritis in two placebo-controlled studies and in an open-label extension study. The safety profile for patients with psoriatic arthritis treated with HUMIRA 40 mg every other week was similar to the safety profile seen in patients with rheumatoid arthritis.

Adverse Reaction Information from Spontaneous Reports:

Adverse events have been reported during post-approval use of HUMIRA. Because these events 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

Hematologic Events: Thrombocytopenia (see **WARNINGS, Hematologic Events**).

Hypersensitivity reactions: Anaphylaxis (see **WARNINGS, Hypersensitivity Reactions).**

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis.

Skin reactions: cutaneous vasculitis.

OVERDOSAGE

The maximum tolerated dose of HUMIRA has not been established in humans. Multiple 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.

DOSAGE AND ADMINISTRATION

The recommended dose of HUMIRA for adult patients with rheumatoid arthritis or psoriatic arthritis is 40 mg administered every other week as a subcutaneous injection. MTX, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics or other DMARDs may be continued during treatment with HUMIRA. In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week.

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

The solution in the syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used. HUMIRA does not contain preservatives;

therefore, unused portions of drug remaining from the syringe should be discarded. NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the pre-filled syringes should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of HUMIRA, according to the directions provided in the Patient Information Leaflet.

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard (see **PATIENT INFORMATION LEAFLET**).

Instructions For Activating the Needle Stick Device: Cartons for institutional use contain a syringe and needle with a needle protection device (see **HOW SUPPLIED**). To activate the needle stick protection device after injection, hold the syringe in one hand and, with the other hand, slide the outer protective shield over the exposed needle until it locks into place.

Storage and Stability

Do not use beyond the expiration date on the container. HUMIRA must be refrigerated at 2-8° C (36-46° F). DO NOT FREEZE. Protect the pre-filled syringe from exposure to light. Store in original carton until time of administration.

HOW SUPPLIED

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

Patient Use Syringe Carton

HUMIRA is dispensed 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 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-02.**

Institutional Use Syringe Carton

Each carton contains two alcohol preps and one dose tray. Each dose tray consists of a single-use, 1 mL pre-filled glass syringe with a fixed 27 gauge ½ inch needle (with a

needle stick protection device) providing 40 mg (0.8 mL) of HUMIRA. **The NDC number is 0074-3799-01.**

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HUMIRA®
(adalimumab)
Patient Information

Read this leaflet carefully before you start taking HUMIRA (**hu-mare-ah**). You should also read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start taking this medicine and at check ups. Talk to your doctor if you have any questions about your treatment with HUMIRA.

What is HUMIRA?

HUMIRA is a medicine that is used in people with moderate to severe rheumatoid arthritis (RA) or with psoriatic arthritis (PsA). RA is an inflammatory disease of the joints. PsA is an inflammatory disease of the joints and skin. People with RA or PsA may be given other medicines for their disease before they are given HUMIRA.

How does HUMIRA work?

HUMIRA is a medicine called a *TNF blocker*, that is a type of protein that blocks the action of a substance your body makes called TNF-alpha. TNF-alpha (tumor necrosis factor alpha) is made by your body's immune system. People with RA or PsA have too much of it in their bodies. The extra TNF-alpha in your body can attack normal healthy body tissues and cause inflammation especially in the tissues in your bones, cartilage, and joints. HUMIRA helps reduce the signs and symptoms of RA (such as pain and swollen joints), may help prevent further damage to your bones and joints, and may help improve your ability to perform daily activities. In addition, HUMIRA helps reduce the signs and symptoms of PsA (such as pain and swollen joints).

HUMIRA can block the damage that too much TNF-alpha can cause, and it can also lower your body's ability to fight infections. Taking HUMIRA can make you more prone to getting infections or make any infection you have worse.

Who should not take HUMIRA?

You should not take HUMIRA if you have an allergy to HUMIRA or to any of its ingredients (including sodium phosphate, sodium citrate, citric acid, mannitol, and polysorbate 80). The needle cover on the pre-filled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.

What information should I share with my doctor before I start taking HUMIRA?

Tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from HUMIRA. If you are unsure, please ask your doctor.

- A history of infections that keep coming back or other conditions that might increase your risk of infections.

- If you have ever had tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor right away. Your doctor will need to examine you for TB and perform a skin test.

- If you experience any numbness or tingling or have ever had a disease that affects your nervous system like multiple sclerosis.

- If you are scheduled to have major surgery.

- If you are scheduled to be vaccinated for anything.

If you are not sure or have any questions about any of this information, ask your doctor.

What important information do I need to know about side effects with HUMIRA?

Any medicine can have side effects. Like all medicines that affect your immune system, HUMIRA can cause serious side effects. The possible serious side effects include:

Serious infections: There have been rare cases where patients taking HUMIRA or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi. Some patients have died when the bacteria that cause infections have spread throughout their body (sepsis).

Nervous system diseases: There have been rare cases of disorders that affect the nervous system of people taking HUMIRA or other TNF blockers. Signs that you could be

experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs and dizziness.

Malignancies: There have been very rare cases of certain kinds of cancer in patients taking HUMIRA or other TNF blockers. People with more serious RA that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take HUMIRA or other TNF blockers, your risk may increase.

Lupus-like symptoms: Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you have chest pains that do not go away, shortness of breath, joint pain or a rash on your cheeks or arms that is sensitive to the sun, call your doctor right away. Your doctor may decide to stop your treatment.

Blood Problems: In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

Heart Problems: You should tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on HUMIRA, or may want to monitor you more closely. If you develop new or worsening problems like shortness of breath or swelling of your ankles or feet, you should call your doctor right away.

Allergic reactions: In rare cases, patients taking HUMIRA have had severe allergic reactions leading to difficulty breathing and low blood pressure, or shock. Allergic reactions can happen after your first dose or may not happen until after you have taken HUMIRA many times. If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away or seek emergency care immediately.

What are the other more common side effects with HUMIRA?

Many patients experience a reaction where the injection was given. These reactions are usually mild and include redness, rash, swelling, itching or bruising. Usually, the rash will go away within a few days. If the skin around the area where you injected HUMIRA still hurts or is swollen, try using a towel soaked with cold water on the injection site. If you have pain, redness or swelling around the injection site that doesn't go away within a

few days or gets worse, call your doctor right away. Other side effects are upper respiratory infections (sinus infections), headache and nausea.

Can I take HUMIRA if I am pregnant or breast-feeding?

HUMIRA has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your health-care provider if you are pregnant, become pregnant or are thinking about becoming pregnant. If you take this medication while you are pregnant, or if you become pregnant while taking HUMIRA you are encouraged to participate in a pregnancy registry to gather additional information about the use of HUMIRA during pregnancy by calling 1-877-311-8972.

Can I take HUMIRA if I am taking other medicines for my RA, PsA or other conditions?

Yes, you can take other medicines provided your doctor has prescribed them, or has told you it is ok to take them while you are taking HUMIRA. It is important that you tell your doctor about any other medicines you are taking for other conditions (for example, high blood pressure medicine) before you start taking HUMIRA.

You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

You should not take HUMIRA with other TNF blockers. If you have questions, ask your doctor.

How do I take HUMIRA?

You take HUMIRA by giving yourself an injection under the skin once every other week, or more frequently (every week) if your doctor tells you to. If you accidentally take more HUMIRA than you were told to take, you should call your doctor. Make sure you have been shown how to inject HUMIRA before you do it yourself. You can call your doctor or the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472) if you have any questions about giving yourself an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

What should I do if I miss a dose of HUMIRA?

If you forget to take HUMIRA when you are supposed to, inject the next dose right away. Then, take your next dose when your next scheduled dose is due. This will put you back on schedule.

Is one time better than another for taking HUMIRA?

Always follow your doctor's instructions about when and how often to take HUMIRA. To help you remember when to take HUMIRA, you can mark your calendar ahead of time with the stickers provided in the back of the patient information booklet. For other information and ideas you can enroll in a patient support program by calling the HUMIRA Patient Resource Center at 1-800-4HUMIRA (448-6472).

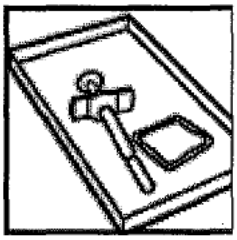
What do I need to do to prepare and give an injection of HUMIRA?

1) Setting up for an injection

- Find a clean flat working surface.
- Remove one dose tray containing a pre-filled syringe of HUMIRA from the refrigerator. Do not use a pre-filled syringe that is frozen or if it has been left in direct sunlight.

You will need the following items for each dose:

- A dose tray containing a pre-filled syringe of HUMIRA with a fixed needle
- 1 alcohol prep



If you do not have all of the pieces you need to give yourself an injection, call your pharmacist. Use only the items provided in the box your HUMIRA comes in.

- Check and make sure the name HUMIRA appears on the dose tray and pre-filled syringe label.
- Check the expiration date on the dose tray label and pre-filled syringe to make sure the date has not passed. Do not use a pre-filled syringe if the date has passed.

- Make sure the liquid in the pre-filled syringe is clear and colorless. Do not use a pre-filled syringe if the liquid is cloudy or discolored or has flakes or particles in it.
- Have a puncture proof container nearby for disposing of used needles and syringes.

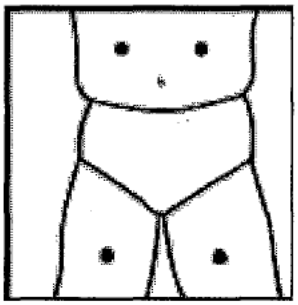
FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

2) Choosing and preparing an injection site

- Wash your hands thoroughly
- Choose a site on the front of your thighs or your abdomen. If you choose your abdomen, you should avoid the area 2 inches around your navel.

  - 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 areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.

  - You may find it helpful to keep notes on the location of previous injections.



- Wipe the site where HUMIRA is to be injected with an alcohol prep, using a circular motion. Do NOT touch this area again until you are ready to inject.

3) How to prepare your HUMIRA dose for injection with a Pre-filled Syringe

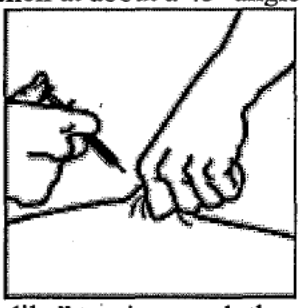
- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line shown on the pre-filled syringe. The top of the liquid may be curved. If the syringe does

not have the correct amount of liquid, DO NOT USE THAT SYRINGE. Call your pharmacist.

- Remove the needle cover taking care not to touch the needle with your fingers or allow it to touch any surface.
- Turn the syringe so the needle is facing up and slowly push the plunger in to push the air in the syringe out through the needle. If a small drop of liquid comes out of the needle that is ok. Do not shake the syringe.

4) Injecting HUMIRA

- With your other hand, gently pinch the cleaned area of skin and hold it firmly. Hold the syringe like a pencil at about a 45° angle to the skin.



- With a quick, short, "dart-like" motion, push the needle into the skin.
- After the needle is in, let go of the skin. Pull back slightly on the plunger, if blood appears in the syringe it means that you have entered a blood vessel. Do not inject HUMIRA. Withdraw the needle and repeat the steps to choose and clean a new injection site. DO NOT use the same syringe; discard it in your puncture proof container. If no blood appears, slowly push the plunger all the way in until all of the HUMIRA is injected.
- When the syringe is empty, remove the needle from the skin keeping it at the same angle it was when it was inserted.
- Press a cotton ball over the injection site and hold it for 10 seconds. Do **NOT** rub the injection site. If you have slight bleeding, do not be alarmed.
- Dispose of the syringe immediately.

5) Disposing of syringes and needles

You should always check with your healthcare provider for instructions on how to properly dispose of used needles and syringes. You should follow any special state or

local laws regarding the proper disposal of needles and syringes. **DO NOT throw the needle or syringe in the household trash or recycle.**

- Place the used needles and syringes in a container made specially for disposing of used syringes and needles (called a "Sharps" container), or a hard plastic container with a screw-on cap or metal container with a plastic lid labeled "*Used Syringes*". Do not use glass or clear plastic containers.
- Always keep the container out of the reach of children.
- When the container is about two-thirds full, tape the cap or lid down so it does not come off and dispose of it as instructed by your doctor, nurse or pharmacist. DO NOT THROW THE CONTAINER IN THE HOUSEHOLD TRASH OR RECYCLE.
- Used preps may be placed in the trash, unless otherwise instructed by your doctor, nurse or pharmacist. The dose tray and cover may be recycled.

HOW DO I STORE HUMIRA?

Store at 2°C – 8°C/36-46°F (in a refrigerator) in the original container until it is used. Protect from light. DO NOT FREEZE HUMIRA. Refrigerated HUMIRA remains sTable until the expiration date printed on the pre-filled syringe. If you need to take it with you, such as when traveling, store it in a cool carrier with an ice pack and protect it from light.

Keep HUMIRA, injection supplies, and all other medicines out of the reach of children.

Revised: ~~July, 2004~~NEW

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

MEDICAL REVIEW(S)

125057/46 09/08/05

CLINICAL REVIEW

Application Type	sBLA
Submission Number	125057/46
Submission Date	December 17, 2004
Receipt Date	December 20, 2004
PDUFA Goal Date	October 20, 2005
Reviewer Name	Alexander Gorovets, M.D.
Review Completion Date	September 8, 2005
Through	Marc Walton, MD, PhD Director DTBIMP
	Jeffrey Siegel, MD Clinical Team Leader
Established Name	HUMIRA
Trade Name	Adalimumab
Therapeutic Class	TNF-α antagonist
Applicant	Abbott Labs
Priority Designation	S
Formulation	Subcutaneous injection
Dosing Regimen	40 mg eow
Indication	moderate to severe RA
Intended Population	moderate to severe RA

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer recommends approving the BLA efficacy supplement STN#: 125057/46 for the use of adalimumab at the recommended doses in patients with moderate to severely active RA with modifications to the proposed labeling.

1.2 Recommendation on Postmarketing Actions

Based on the review of the efficacy supplement, no new postmarketing studies will be required as no new safety signals have been identified in this trial and no new questions regarding lack of efficacy have been raised.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This was a multi-center, randomized, double-blind, active comparator-controlled, parallel-group, Phase III study of adalimumab in MTX-naïve subjects with early RA (defined as RA meeting American College of Rheumatology criteria and disease duration of less than 3 years). Subjects were randomized 1:1:1 to one of three treatment groups: adalimumab 40 mg eow, adalimumab 40 mg eow together with weekly MTX (≤20 mg/week), or weekly MTX (≤20 mg/week). Adalimumab administration was subcutaneous while MTX was given orally. The study was conducted at 132 sites and involved 799 randomized subjects and a two-year blinded treatment period. There were two primary efficacy endpoints. The first primary endpoint was clinical and consisted of the proportion of subjects who achieved an ACR50 response at Week 52 in the adalimumab + MTX combination therapy arm as compared to that achieved in the MTX monotherapy arm. The second primary endpoint was radiographic and consisted of the change from Baseline in modified Total Sharp Score (TSS) at week 52. If the first primary endpoint was met, the second primary endpoint was analyzed to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression. The scheduled assessments constituting the measurement of a clinical response and the safety assessments of adverse events took place on Weeks 0, 2, 4, 8, 12, 16, 20, 24, 26, 34, 42, 50, and 52 during the first blinded year of study, and every 8 weeks during the second year. The scheduled radiographic assessments took place at Baseline, Week 26, 52, and 104. The two paired blinded radiographic readers were each presented with image sets for each patient in a specified order. The readers remained blinded to the chronologic order and the treatment arm from which a given radiographic set originated.

1.3.2 Efficacy

In subjects with recently diagnosed moderate to severe RA, adalimumab + MTX combination therapy, as compared to MTX monotherapy, resulted in a greater improvement of signs and symptoms, as measured by the proportion of subjects who achieved an ACR50 response, and in a greater inhibition of radiographic progression, as measured by the change from Baseline in modified TSS. Among the subjects receiving Adalimumab+MTX combination therapy, 62% achieved an ACR50 response after 52 weeks of treatment, and the mean change in the modified Total Sharp Score was 1.3. In comparison, among the subjects receiving MTX monotherapy, 46% achieved an ACR50 response (p-value < 0.001), and the mean change in the modified TSS was 5.7 (p-value < 0.001).

Following up to 104 weeks of treatment, adalimumab + MTX combination therapy, as compared to MTX monotherapy, resulted in greater improvement of physical function, greater improvement of signs and symptoms, greater inhibition of radiographic progression, greater achievement of the lower activity disease state, greater achievement of a major clinical response, and greater improvement in the physical components of a patient reported outcome assessment scale. The findings were clinically and statistically significant.

The greater treatment effect of adalimumab + MTX combination therapy on clinical and radiographic response at Week 52, as compared to MTX monotherapy, was consistent across all analyzed subgroups in which a sufficient number of subjects were included.

Review of the efficacy data from all three treatment arms indicated that, whereas improvement could be seen in each treatment arm, the greatest improvement occurred in the combination arm. Adalimumab + MTX combination therapy resulted in a greater improvement than either monotherapy in signs and symptoms, inhibition of radiographic progression, improvement in physical function, and induction of major clinical response over two years of the double-blind treatment.

1.3.3 Safety

A total of six deaths occurred during the trial of adalimumab in patients with RA of recent onset: one in the MTX monotherapy arm, one in the adalimumab + MTX combination treatment arm, and four in the adalimumab monotherapy arm. None of the causes of mortality appeared to represent a new safety signal for the use of adalimumab in patients with rheumatoid arthritis. Fifteen cases of malignancy were observed during this two-year controlled trial: five in MTX monotherapy arm, six in adalimumab + MTX combination treatment arm, and four in adalimumab monotherapy arm. The types of malignancy observed in this study were the types one would expect to observe in this patient population. Serious infectious adverse events (AEs) were reported at a higher frequency in subjects receiving adalimumab + MTX combination therapy than in those receiving monotherapy with either agent. However, the 5% rate of serious infectious AEs observed over 2 years was within the range of serious infections reported in

patients with untreated RA. The types of serious infectious AEs reported in this clinical trial were comparable across three treatment arms, with the most frequent ones being pneumonia, cellulitis and septic arthritis. Three subjects, all in the adalimumab + MTX treatment group, developed tuberculosis (TB) during their participation in the study. No other opportunistic infections were reported in this study. No demyelinating events were reported. One case of a lupus-like reaction was reported in a subject receiving adalimumab monotherapy. Two cases of congestive heart failure were reported, one in each of the monotherapy arms.

The adverse events that were observed in this study were already adequately described in the adalimumab label and no new safety signals were identified. However, safety concerns developed as a result of the review of the concurrently submitted Labeling Supplement and involved new information on the incidence of malignancy in the controlled portions of HUMIRA trials.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of the clinical data for the review of efficacy consisted of 1 Abbott-sponsored randomized, controlled clinical trial conducted in the United States, Europe, Australia, and New Zealand (STN 125057/46). The sources of the clinical data for the integrated safety review consisted of the safety data presented by the sponsor in the Efficacy supplement (STN 125057/46), and of the safety data submitted in the Labeling supplement (STN 125057/58), as well as the data presented by the sponsor in response to the FDA requests for information and submitted as amendments to these supplements.

4.4. Data Quality and Integrity

Two representative sites, both in the US, were inspected by the FDA. There was sufficient documentation to assure that all audited study subjects did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements. The data submitted in support of this BLA appeared acceptable. The amount of missing data was low. FDA statistician verified the analyses of the primary and the major secondary endpoints. FDA imaging reviewers verified the radiographic data and concurred with its interpretation.

4.6. Financial Disclosures

Financial disclosure was reviewed and appeared to be complete. The sites with the investigators identified by the sponsor as having a financial interest in Abbott accounted for less than 3% of the subject population enrolled in this study.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Indication

The current indication for adalimumab in the US for Rheumatoid Arthritis is as follows: "HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. HUMIRA can be used alone or in combination with MTX or other DMARDs". The sponsor proposes to revise the current indication statement to insert "inducing major clinical response", and in describing the RA patients, to remove the phrase "who have had an inadequate response to one or more DMARDs" and replace it with the phrase [redacted] (b) (4), [redacted] (b) (4).

6.1.2 General Discussion of Endpoints

This study has two co-primary endpoints: improvement in signs and symptoms as assessed by ACR50 at Week 52, and prevention of structural damage as assessed by a change from Baseline in the modified Total Sharp Score at Week 52. These two co-primary endpoints are consistent with the RA guidance document to adequately assess the efficacy of a drug in patients with RA and to demonstrate the durability of the effect since the proposed treatment will be administered chronically. The durability of the treatment group response is being further evaluated by the performance of the same endpoint assessment at Week 104.

In comparison to a more traditionally used ACR20, achieving an ACR50 response represents a more robust measure of clinical response in evaluating the treatment of RA. An ACR50 response is a more clinically relevant measure by which to gauge a therapy's response, especially in a trial with MTX-naïve subjects that uses an active comparator, such as MTX, which would project a higher response rate in the control arm.

In reference to the radiographic assessment, the modified TSS is commonly utilized and accepted in the evaluation of joint damage.

As the reduction in synovial inflammation may confer additional clinical benefits, measuring other laboratory and patient-reported outcomes (see secondary endpoints) adds to the robustness of the conclusions drawn from the analyses of the primary endpoints.

Given that MTX is a slow-acting DMARD, the primary efficacy assessment at Week 52 provides for treatment duration that allows a clinically meaningful comparison between treatment groups.

6.1.3 Study Design

This was a multi-center, randomized, double-blind, active comparator-controlled, parallel-group, Phase III study of adalimumab in MTX-naïve subjects with early RA (defined as RA meeting American College of Rheumatology criteria and disease duration of less than 3 years). Subjects were randomized 1:1:1 to one of three treatment groups: adalimumab 40 mg eow, adalimumab 40 mg eow together with weekly MTX (≤20 mg/week), or weekly MTX (≤20 mg/week). Adalimumab administration was subcutaneous while MTX was given orally. Effective therapeutic doses of MTX, ≥ 7.5 mg/week to ≤ 20 mg/week, were utilized, with the optimization of the MTX dose to be completed within 8 weeks. The study was conducted at 132 sites and involved 799 randomized subjects and a two-year blinded treatment period.

The study's objective was to compare adalimumab + MTX combination therapy with MTX monotherapy. There were two primary efficacy endpoints. The first primary endpoint was clinical and consisted of the proportion of subjects who achieved an ACR50 response at Week 52 in the adalimumab + MTX combination therapy arm as compared to the one achieved in MTX monotherapy arm. The second primary endpoint was radiographic and consisted of the change from Baseline in modified TSS at week 52. If the first primary endpoint was met, the second primary endpoint was analyzed to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression.

Main entry criteria required that subjects be ≥ 18 years with a diagnosis of active RA (≥ 8 swollen joints out of 66 joints assessed and ≥ 10 tender joints out of 68 joints assessed) with disease duration < 3 years. Subjects were not to have received previous treatment with MTX, cyclophosphamide, cyclosporine, azathioprine, or more than two other DMARDs. Other major eligibility requirements included erythrocyte sedimentation rate ≥ 28 mm/h or C-reactive protein (CRP) ≥ 1.5 mg/dL, at least 1 joint erosion or positive rheumatoid factor, no oral prednisone or prednisone equivalent > 10 mg/day within 30 days, and no intra-articular or parenteral administration of corticosteroids in the preceding 6 weeks.

The scheduled assessments constituting the measurement of a clinical response and the safety assessments of adverse events took place on Weeks 0, 2, 4, 8, 12, 16, 20, 24, 26, 34, 42, 50, and 52 during the first blinded year of study, and every 8 weeks during the second year. The scheduled radiographic assessments took place at Baseline, Week 26, 52, and 104.
The review of radiographs was independently conducted by Bio-Imaging Technologies, Inc. (BITI), an independent Contract Research Organization. The clinical trial sites forwarded the images to BITI for data processing and preparation for the independent readings that were performed by two paired readers. Each reader was presented with image sets for each patient in the following order: right hand-wrist and foot and then left hand-wrist and foot. There were two to four time points for each image set but the order of the time points was randomized. The readers remained blinded to the chronologic order and the treatment arm from which a given radiographic set originated.

The primary analysis population consisted of all subjects who were randomized and who received at least one dose of double-blinded study medication (Full Analysis Set). No

randomized subjects were excluded from the efficacy analyses. The primary analysis of the first primary endpoint was conducted using the methodology of the Non-responder (NR) imputation of the missing data. The second primary analysis was performed once the first primary objective was met. The analysis of this second conditional primary endpoint was based on the pre-specified approach of using a linear imputation method for missing data (see Appendix).

The major secondary endpoints that compared the combination treatment with MTX monotherapy were pre-specified and analyzed using the Full Analysis Set in the conditional manner in the following specified order: Change from Baseline in the Disability Index of HAQ at Week 52; ACR50 Response at Week 104; Change from Baseline in Modified Total Sharp Score at Week 104; Subjects in Clinical Remission as Defined by DAS28 <2.6 at Week 52; Change from Baseline in the Physical Component of SF-36 at Week 52; Major Clinical Response (ACR70) Over 104 Weeks of Treatment; and Change from Baseline in the Mental Component of the SF-36 at Week 52. Among the clinical categories that were assessed in all three treatment arms the following categories were reflected in the labeling: Signs and Symptoms; Radiographic Progression, or Structural Damage; and Physical Function.

6.1.4 Efficacy Findings

6.1.4.1 Study Conduct

All 799 randomized subjects received study medication. The review of blinding procedures found them to be adequate. No major protocol violations were present. The median dose of MTX achieved in each of the MTX containing arms was 20 mg/week.

As shown in Table 1, the proportion of subjects completing the 52 weeks of treatment in the Adalimumab+MTX combination group exceeded that of either monotherapy group. Whereas, by 52 weeks, only 18% of subjects in the combination treatment group terminated the study prematurely, 29% and 24% of subjects withdrew from the study in the Adalimumab and MTX monotherapy groups respectively.

Table 1.Patient Disposition at Week 52

	MTX (N =257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Number of subjects completing 52 weeks, n (%)	196 (76)	194 (71)	220 (82)
Subjects who prematurely terminated	61 (24)	80 (29)	48 (18)

Table 2.Reasons for Discontinuation by Week 52

	MTX (N =257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Subjects who prematurely terminated, n	61	80	48
Planned selection criteria, n (%)	0	1 (<1)	0
Adverse Event, n (%)	14 (5)	19 (7)	22 (8)
Protocol violation, n (%)	4 (2)	2 (1)	2 (1)
Death, n (%)	1 (<1)	1 (<1)	0
Withdrew consent, n (%)	8 (3)	13 (5)	7 (3)
Lack of efficacy and/or progression of disease, n (%)	32 (12)	43 (16)	12 (5)
Administrative reasons, n (%)	2 (1)	1 (<1)	5 (2)

The reasons for study treatment discontinuation are presented in Table 2. Whereas a somewhat higher number of subjects in the combination treatment group discontinued due to an adverse event, a higher proportion of subjects discontinued due to lack of efficacy in each monotherapy group than in the Adalimumab+MTX group. Other reasons for discontinuation were low in frequency and comparable between the groups. At week 104, in the combination treatment group, 76% of randomized subjects completed the study treatment (see Table 3). In the Adalimumab and MTX monotherapy groups, 61% and 66% respectively completed the study treatment.

Table 3.Patient Disposition at week 52 and week 104

	MTX	Adalimumab	Adalimumab + MTX
Baseline, n (%)	257 (100)	274 (100)	268 (100)
Week 52	196 (76)	194 (71)	220 (82)
Week 104	169 (66)	167 (61)	203 (76)

In concert with the aforementioned disposition of the clinical data, for the disposition of the radiographic data, as shown in Table 4, the films were missing at week 104 in 24% of subjects randomized to the Adalimumab+MTX combination treatment group, in 39% of subjects randomized to the Adalimumab group and in 33% of subjects in the MTX group.

Table 4.Disposition of Radiographic Data

Number (%) of Subjects with missing films	MTX Monotherapy (N = 257)	Adalimumab Monotherapy (N = 274)	Adalimumab+MTX Combination (N = 268)
at Baseline			
n (%)	6 (2)	3 (1)	1 (<1)
at Week 26			
n (%)	38 (15)	44 (16)	27 (10)
at Week 52			
n (%)	52 (20)	69 (25)	38 (14)
at Week 104			
n (%)	84 (33)	108 (39)	65 (24)

The number of subjects who had a baseline and at least one post-baseline film was comparable between the treatment groups (see Appendix Table), with 97% of subjects in the combination treatment group and 93% in each of the monotherapy groups providing data that consisted of a baseline and at least one post-baseline film.

6.1.4.2 Study Demographics

As demonstrated in the following five tables, the demographics and the disease characteristics of the study subjects were reflective of a MTX naive RA population with moderately to severely active disease of recent onset. The review of the data presented in these tables confirmed that the study arms were well balanced in that the demographics and the disease characteristics were comparable across the treatment arms. The mean age of the randomized subjects was 52 years, the mean weight was 75kg, 75% of subjects were female, 93% were white, and 68% had not previously received a DMARD for the treatment of their RA. The types of DMARDs received by the study subjects were typical for this patient population, with the prominent use of Sulfasalazine being reflective of the preponderance of the European sites. The mean and median

duration of RA from the time of diagnosis was 9 months and 5 months respectively. The mean tender joint count was 33 and the mean swollen joint count was 22. The overall activity score, as measured by the DAS28, was 6.3, indicating high disease activity.

Table 5.Baseline Demographics

Demographic Characteristic	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Age (years)			
Mean ± SD	52.0 ± 13.1	52.1 ± 13.5	51.9 ± 14.0
Age group, n (%)			
<40	43 (17)	54 (20)	52 (19)
40 - 64	169 (66)	173 (63)	161 (60)
65 - 74	33 (13)	36 (13)	42 (16)
≥75	12 (4)	11 (4)	13 (5)
Sex, n (%)			
Female	190 (74)	212 (77)	193 (72)
Male	67 (26)	62 (23)	75 (28)
Race, n (%)			
White	242 (94)	256 (93)	250 (93)
Black	7 (3)	8 (3)	8 (3)
Asian	1 (<1)	3 (1)	6 (2)
Other	7 (3)	7 (3)	4 (2)
Body weight (kg)			
Mean ± SD	75.5 ± 17.9	74.4 ± 17.8	76.8 ± 17.9

Table 6.Previous DMARD therapy (by numbers)

Number of previous DMARDs used, n (%)	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
0	176 (68)	183 (67)	181 (68)
1	64 (25)	71 (26)	69 (26)
2	17 (7)	20 (7)	17 (6)
>2	0	0	1 (<1)

Table 7.Previous DMARD therapy (by type)

	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Number of subjects taking previous DMARDs	81	91	87
Anti-malarials n (%)	39 (40)	39 (35)	52 (49)
Azathioprine n (%)	0	1 (1)	1 (1)
Gold preparations n (%)	11 (11)	11 (10)	6 (6)
Leflunomide n (%)	10 (10)	12 (11)	4 (4)
Methotrexate n (%)	0	1 (1)	0
Minocycline n (%)	1 (1)	3 (3)	1 (1)
Sulfasalazine n (%)	37 (38)	43 (39)	42 (39)

Table 8.Baseline Disease Characteristics

Disease Characteristic	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab +MTX (N = 268)
Duration of RA (years)			
Mean ± SD	0.8 ± 0.9	0.7 ± 0.8	0.7 ± 0.8
Median (range)	0.4 (0.0 - 3.2)	0.4 (0.0 - 3.8)	0.4 (0.0 - 3.1)
Duration of RA, n (%)			
0.0 - 0.5, years	138 (54)	160 (58)	156 (58)
0.5 - 1.0, years	37 (14)	40 (15)	42 (16)
1.0 - 2.0, years	42 (16)	43 (16)	41 (15)
2.0 - 3.0, years	36 (14)	26 (9)	27 (10)
≥ 3.0, years	4 (2)	5 (2)	2 (1)
Baseline corticosteroid use, n (%)			
Yes	91 (35)	100 (36)	96 (36)
No	166 (65)	174 (64)	172 (64)
Baseline RF, n (%)			
Negative	41 (16)	45 (16)	40 (15)
Positive	215 (84)	227 (83)	228 (85)
Missing	1 (<1)	2 (1)	0

Table 9.Disease Activity Parameters at Baseline (Mean ± SD except where noted)

Efficacy Parameter	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Tender Joint Count (68)	32 ± 14	32 ± 14	31 ± 14
Swollen Joint Count (66)	22 ± 12	22 ± 11	21 ± 11
C-reactive protein (mg/dL)			
Mean ± SD	4.0 ± 4.0	4.1 ± 3.9	3.9 ± 4.2
Median	2.6	2.7	2.4
Disability Index of HAQ	1.48 ± 0.67	1.63 ± 0.62	1.47 ±0.64
DAS28-4 (including general health)	6.335 ± 0.873	6.367 ± 0.921	6.304 ± 0.937
FACIT-F	29.0 ± 11.1	26.2 ± 11.3	28.4 ± 11.7
HUI 2	0.61 ± 0.20	0.59 ± .21	0.62 ± 0.20
HUI 3	0.39 ± 0.27	0.33 ± 0.28	0.39 ± 0.29
SF-36 Physical component	29.6 ± 8.2	28.0 ±7.7	29.1 ± 8.1
SF-36 Mental component	44.4 ± 12.1	43.5 ± 11.8	45.0 ± 12.2
PGA of Disease Activity (100 mm VAS)	65.6 ± 17.7	67.6 ± 18.6	65.1 ± 17.6
PaGA of Disease Activity (100 mm VAS)	63.0 ± 25.0	67.8 ± 23.3	66.8 ± 22.1
Patient's assessment of Pain (100 mm VAS)	59.6 ± 24.3	64.6 ± 23.6	62.5 ± 21.3
Morning Stiffness, n (%)			
Yes	252 (98)	267 (97)	263 (98)
No	5 (2)	7 (3)	5 (2)
Duration of morning stiffness (minutes)	143 ± 114	142 ± 104	134 ±107
Modified TSS	21.9 ± 22.2	18.8 ± 19.0	18.1 ± 20.1
Erosion Score	13.6 ± 13.6	11.3 ± 11.3	11.0 ± 12.3
Joint Space Narrowing Score	8.2 ± 10.7	7.5 ± 9.4	7.1 ± 9.6
Subjects with at least one erosion at baseline, n (%)	246 (96)	258 (94)	248 (93)

6.1.4.3 Efficacy Analyses Based on the Primary Endpoints

Clinical Response

At week 52, 62% of subjects receiving Adalimumab+MTX combination therapy achieved an ACR50 response compared to 46% of subjects receiving MTX monotherapy ($p<0.001$; Table 10). The primary efficacy analysis was performed using the non-responder method of imputation of the missing data. The sensitivity analyses (see Table 11) included the LOCF method for imputing of the missing data as well a method of analyzing the data as observed, without any imputation of the missing data. Both of these sensitivity analyses were consistent with the results obtained using the primary analysis methodology.

Table 10.Primary Efficacy Analysis-ACR50 Response at Week 52

	MTX (257)	Adalimumab + MTX (N = 268)	p-value (a)
Week 52, n (%)	118 (46)	165 (62)	<0.001

(a) P-value is from a comparison between adalimumab + MTX combination therapy and MTX monotherapy using Pearson's chi-square test.

Table 11.Sensitivity Analyses-ACR50-Responses at Week 52

	MTX (257)	Adalimumab + MTX (N = 268)	p-value (a)
Observed			
Number of Evaluable Subjects	195	220	
Week 52 Responders, n (%)	118 (61)	165 (75)	0.002
LOCF			
Number of Evaluable Subjects	257	268	
Week 52 Responders, n (%)	118 (46)	166 (62)	<0.001

(a) P-value is from a comparison between adalimumab + MTX combination therapy and MTX monotherapy using Pearson's chi-square test

Radiographic Response

In the combination treatment group, the mean modified Total Sharp Score at baseline was 18.1 (see Table 12). The smaller the changes in the score that occur over a period of time the less radiographic progression, or less structural damage, there is over the same period. Utilizing the pre-specified linear imputation method for the missing data in the primary analysis of the

radiographic response data, the mean change in the modified Total Sharp Score at week 52 was 1.3. In comparison, the mean change in the modified Total Sharp Score at week 52 in the MTX monotherapy group was 5.7. The difference was statistically significant at a p-value of <0.001. A benefit of Adalimumab+MTX over MTX alone was also seen when the data were expressed as median rather than mean values of the modified TSS. (The FDA radiologists, Drs. Ju and Martynec, reviewed the X-ray readings and validated the scores).

Table 12.Change in Modified Total Sharp Score from Baseline at Week 52

	MTX (N=257)		**Adalimumab + MTX (N=268)**		**p-value (a)**
	Mean ± SD	Median	Mean ± SD	Median	
Baseline	21.8 ± 22.2	15.5	18.1 ± 20.1	13.3	
Change at Week 52	5.7 ± 12.7	2.5	1.3 ± 6.5	0.0	<0.001

(a) P-value is from the pairwise comparison of adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.

Four sensitivity analyses of the radiographic response data were performed, as shown in Table 13. They confirmed the results of the primary analysis.

Table 13.Sensitivity Analyses / TSS / Week 52

	MTX (N = 257)		**Adalimumab + MTX (N = 268)**		**p-value (a)**
	Mean ± SD	Median	Mean ± SD	Median	
Observed					
Baseline	22.2 ±22.5	15.8	18.6 ± 20.6	13.0	
Change at Week 52	5.2 ± 9.4	2.0	1.0 ± 3.2	0.0	<0.001
LOCF					
Baseline	21.6 ± 22.1	15.5	18.2 ± 20.2	12.8	
Change at Week 52	5.2 ± 9.3	2.0	1.0 ± 3.3	0.0	<0.001
ANOVA (b)					
Baseline	22.2 ± 22.5	15.8	18.6 ± 20.6	13.0	
Change at Week 52	5.2 ± 9.4	2.0	1.0 ± 3.2	0.0	<0.001

75th Percentile (c)					
Baseline	21.9 ± 22.2	15.5	18.1 ± 20.1	13.0	
Change at Week 52	4.8 ± 8.4	3.5	1.3 ± 3.1	0.5	<0.001

(a) P-value is from the pairwise comparison of adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.
(b) Mean changes were compared between treatment groups using a one-way analysis of variance
(c) The missing change from Baseline values for TSS was imputed using the 75th percentile of the non-missing change from Baseline scores for the two treatment groups.

6.1.4.4. Efficacy Analyses Based on the Major Secondary Endpoints.

The Disability Index of the Health Assessment Questionnaire (HAQ-DI) was utilized for the measurement of changes in the physical function of subjects undergoing study treatment. An improvement in the HAQ-DI score is represented by a negative change over a period of time. As shown in Table 14, following 52 weeks of treatment, adalimumab + MTX combination therapy resulted in a negative change of 1.1units whereas MTX monotherapy resulted in a negative change of 0.8 units, with the difference being statistically significant at p-value <0.001.

Table 14.Change in the Disability Index of the HAQ Score (Mean ± SD) from Baseline to Week 52

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value(a)
N	191	213	
Baseline	1.5	1.5	
Week 52	0.7	0.4	
Change at Week 52	-0.8± 0.6	-1.1± 0.6	<0.001

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.

As shown in Table 15, following 104 weeks of treatment and in accordance with the primary analysis methodology, 59% of subjects undergoing Adalimumab+MTX combination therapy achieved an ACR50 response compared to 43% of subjects in the MTX monotherapy group ($p<0.001$). The results of the sensitivity analyses were consistent with the primary analysis results.

Table 15.ACR50 Response at Week 104

ACR50 at Week 104	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value
Non-responder imputation			
Week 104 responders, n (%)	110 (43)	158 (59)	<0.001(a)
Observed			
Number of Evaluable Subjects	168	203	
Week 104 Responders, n (%)	110 (66)	158 (78)	0.008(b)
LOCF			
Number of Evaluable Subjects	257	268	
Week 104 Responders, n (%)	116 (45)	168 (63)	<0.001(b)

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the chi-square test.
(b) P-value is from a comparison between Adalimumab + MTX combination therapy and MTX monotherapy using Pearson's chi-square test

Following 104 weeks of treatment (see Table 16), subjects treated with adalimumab + MTX combination therapy had a mean increase in the modified TSS from Baseline of 1.9 Sharp units compared to 10.4 Sharp units in subjects treated with MTX monotherapy ($p<0.001$).

Table 16.Change from Baseline in Modified TSS at Week 104

	MTX (N = 257)	Adalimumab + MTX (N = 268)	P-value (a)
Linear Extrapolation			
Change at Week 104 (mean ± SD)	10.4 ± 21.7	1.9 ± 8.3	<0.001
As Observed (N)	172	202	
Change at Week 104 (mean ± SD)	6.4 ± 11.8	1.1 ± 4.0	<0.001
LOCF (N)	220	244	
Change at Week 104 (mean ± SD)	7.0 ± 12.3	1.2 ± 4.1	<0.001

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.

Table 17 presents the percent of patients achieving very low disease activity, based on the DAS28. The DAS28 has a scale from 0 to 10 indicating the current activity of RA. According to European League Against Rheumatism (EULAR) criteria, DAS28 > 5.1 indicates high disease activity and DAS28 < 3.2 indicates low disease activity. "Clinical remission" is defined by EULAR as DAS28 < 2.6. FDA does not accept it as a definition of remission because patients meeting these criteria can nonetheless have several tender or swollen joints. Following 52 weeks of treatment, 43% of subjects who received the combination therapy achieved low disease activity compared to 21% of subjects who received MTX monotherapy (p<0.001).

Table 17.Subjects in EULAR Defined Clinical Remission at Week 52

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value (a)
Subjects with DAS28 < 2.6 at week 52, n (%)	53 (21)	115 (43)	<0.001

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the chi-square test.

As shown in Table 18, following 52 weeks of treatment, subjects who received adalimumab + MTX combination therapy demonstrated a mean increase of 16.0 units from baseline in the physical component of the SF-36 compared to an increase of 11.8 in subjects who received MTX monotherapy, which was statistically significant.

Table 18.Change from Baseline (Mean ± SD) in Physical Components of SF-36 at Week 52

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value(a)
LOCF subjects at Baseline, n	247	256	
Baseline Score	29.6 ± 8.2	29.1 ± 8.1	
LOCF subjects at Week 52, n	208	232	
Change in Score at Week 52	11.8 ± 9.8	16.0 ± 10.3	<0.001

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the Wilcoxon test.

"Major clinical response" is defined as a continuous ACR70 response for 6 continuous months. As demonstrated in Table 19, following 104 weeks of treatment, 49% of subjects who received adalimumab + MTX combination therapy achieved a major clinical response, compared to 27% of subjects who received MTX monotherapy (p<0.001).

Table 19.Major Clinical Response Over 104 Weeks of Treatment

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value (a)
Subjects with major clinical response at Week 104, n (%)	70 (27)	130 (49)	<0.001

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the chi-square test.

In reference to the mental component of SF-36, as in Table 20, following 52 weeks of treatment, similar improvements were seen in subjects treated with adalimumab + MTX combination therapy compared to subjects treated with MTX monotherapy. Of note, both treatment groups had high baseline mental component scores, leaving a relatively small range for further improvement.

Table 20.Change from Baseline (Mean ± SD) in Mental Components of SF-36 at Week 52.

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value(a)
LOCF subjects at Baseline, n	247	256	
Baseline Score	44.4 ± 12.1	45.0 ± 12.2	
LOCF subjects at Week 52, n	208	232	
Change in Score at Week 52	6.7 ± 11.2	7.0 ± 12.7	0.664

(a) P-value is from the pairwise comparison of Adalimumab + MTX combination therapy and MTX monotherapy using the Wilcoxon test.

In Tables 14 through 20, the data for the major secondary analyses were presented in the pre-specified order as described in the Study Design section on page 7. All of the major secondary endpoints showed statistical superiority of adalimumab + MTX combination therapy compared to MTX monotherapy with the exception of the last, the mental component of the SF-36 at Week 52.

6.1.4.5 Other Secondary Analyses

Improvement in Signs and Symptoms

A summary of ACR20, ACR50 and ACR70 response rates at Weeks 52 and 104 are presented in Table 21. ACR responses at Weeks 52 and 104 provide a consistent pattern of greater improvements in the adalimumab + MTX combination therapy group compared to either the MTX or the adalimumab monotherapy group.

Table 21. ACR 20 / 50 / 70 at Weeks 52 and 104
(Non-Responder Imputation)

	MTX (N = 257)	Adalimumab (N = 274)	**Adalimumab +MTX (N= 268)**	**p-value (a)**	p-value (b)
	n (%)	n (%)	**n (%)**		
ACR20					
Week 52	**161 (63)**	149 (54)	**195 (73)**	**0.013**	<0.001
Week 104	**144 (56)**	135 (49)	**186 (69)**	**0.002**	<0.001
ACR50					
Week 52	**118 (46)**	113 (41)	**165 (62)**	**<0.001**	<0.001
Week 104	**110 (43)**	101 (37)	**158 (59)**	**<0.001**	<0.001
ACR70					
Week 52	**70 (27)**	71 (26)	**122 (46)**	**<0.001**	<0.001
Week 104	**73 (28)**	77 (28)	**125 (46)**	**<0.001**	<0.001

(a) P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.
(b) P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using Pearson's chi-square test.

Components of the ACR response criteria were compared between treatment groups. These assessments included Tender Joint Count (TJC), Swollen Joint Count (SJC), Disability Index of the Health Assessment Questionnaire, Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, and a CRP level. A summary of the change from Baseline in the ACR core components at Weeks 52 and 104 is presented in Table 22.

Table 22. ACR Core Components (Median) at Week 52 and Week 104

(LOCF Analysis)

	MTX	A	A + MTX	p-value (a)	p-value (b)
Tender Joint Count					
Baseline	31	30	29		
Change at Week 52	-19	-18	-21	0.021	0.003
Change at Week 104	-18	-19	-21	0.026	0.004
Swollen Joint Count					
Baseline	19	20	18		
Change at Week 52	-12	-11	-14	0.006	< 0.001
Change at Week 104	-12	-12	-15	0.001	< 0.001
HAQ-DI					
Baseline	1.5	1.6	1.5		
Change at Week 52	-0.6	-0.6	-1.0	< 0.001	< 0.001
Change at Week 104	-0.6	-0.6	-1.0	< 0.001	< 0.001
PAP (100 mm VAS)					
Baseline	62	70	65		
Change at Week 52	-35	-32	-48	< 0.001	< 0.001
Change at Week 104	-32	-31	-48	< 0.001	< 0.001
PGA (100mmVAS)					
Baseline	66	73	70		
Change at Week 52	-36	-34	-51	<0.001	<0.001
Change at Week 104	-33	-34	-50	<0.001	<0.001
PHGA(100mmVAS)					
Baseline	69	70	68		
Change at Week 52	-44	-43	-53	<0.001	<0.001
Change at Week 104	-43	-43	-53	<0.001	<0.001
CRP (mg/dL)					
Baseline	2.6	2.7	2.4		
Change at Week 52	-1.3	-0.8	-1.7	0.004	<0.001
Change at Week 104	-1.3	-0.8	-1.7	0.005	<0.001

(a) P-value from the Wilcoxon test comparing MTX monotherapy and adalimumab + MTX combination therapy, unadjusted for multiple comparisons
(b) P-value from the Wilcoxon test comparing adalimumab monotherapy and adalimumab + MTX combination therapy, unadjusted for multiple comparisons
Abbreviations: A – Adalimumab; HAQ-DI – Health Assessment Questionnaire-Disability Index; PAP – Patient's Assessment of Pain; PGA – Patient's Global Assessment of Disease Activity; PHGA – Physician's Global Assessment of Disease Activity; VAS – Visual Analogue Scale

Inhibition in Progression of Structural Damage

A summary of the change from Baseline in modified TSS at Weeks 52 and 104 is presented in Table 23. An increase in modified TSS is indicative of worsening of joint damage. Missing data were imputed according to the pre-specified rules of linear extrapolation (see Appendix).

Table 23. Change from Baseline (Mean ± SD) In the Modified TSS and Components of the Modified TSS at Weeks 52 and 104

	MTX (N = 257)	Adalimumab (N = 274	**Adalimumab + MTX (N = 268)**	**p-value (a)**	p-value (b)
Modified TSS					
Baseline	**21.8 ± 22.2**	18.8 ± 19.0	**18.1 ± 20.1**		
Change at Week 52	**5.7 ± 12.7**	3.0 ± 11.2	**1.3 ± 6.5**	**<0.001**	0.002
Change at Week 104	**10.4 ± 21.7**	5.5 ± 15.8	**1.9 ± 8.3**	**<0.001**	<0.001
Erosion score					
Baseline	**13.6**	11.3	**11.0**		
Change at Week 52	**3.7 ± 8.4**	1.7 ± 5.7	**0.8 ± 3.3**	**<0.001**	0.008
Change at Week 104	**6.4 ± 14.3**	3.0 ± 8.3	**1.0 ± 4.7**	**<0.001**	<0.001
JSN score					
Baseline	**8.2**	7.5	**7.1**		
Change at Week 52	**2.0 ± 6.3**	1.3 ± 6.6	**0.5 ± 4.2**	**<0.001**	<0.004
Change at Week 104	**4.0 ± 10.9**	2.6 ± 9.5	**0.9 ± 5.1**	**<0.001**	<0.001

(a) P-value is from the pairwise comparison of MTX monotherapy and Adalimumab + MTX combination therapy using the Mann-Whitney U test.
(b) P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

As shown in Table 23, at Week 52, subjects treated with MTX monotherapy had a mean increase of 5.7 units in the modified TSS. Treatment with adalimumab monotherapy for 52 weeks resulted in a smaller mean increase of 3.0 units, and treatment with adalimumab + MTX combination resulted in a mean increase of 1.3 units, a result which was clinically and statistically superior to either monotherapy treatment group. At Week 104, subjects treated with MTX monotherapy had a mean increase of 10.4 units in the modified TSS. Treatment with adalimumab monotherapy for 104 weeks resulted in a smaller mean increase of 5.5 units, and treatment with adalimumab + MTX combination resulted in a mean increase of 1.9 units, a result which was statistically significant in comparison to either monotherapy treatment group. Given that estimated yearly x-ray progression is 4 – 8 units in untreated patients, these differences are also clinically significant. In reference to the analysis of the change in the components of the modified Total Sharp Score, at Week 52, subjects treated with MTX monotherapy had a mean increase from Baseline of 3.7 in Erosion score. Treatment with adalimumab monotherapy for 52 weeks resulted in a smaller mean increase of 1.7 in Erosion score, and treatment with adalimumab + MTX combination resulted in a mean increase in Erosion score of 0.8, a result which was superior to either monotherapy treatment group. Erosion score data showed similar results. Subjects treated with MTX monotherapy had a mean increase in Joint Space Narrowing (JSN) score of 2.0 at Week 52 from Baseline. Treatment with adalimumab monotherapy for 52 weeks resulted in a smaller mean increase of 1.3 in JSN score, and treatment with adalimumab + MTX combination resulted in a mean increase in JSN score of only 0.5, a result which was statistically significant in comparison to either monotherapy treatment group. Similar reductions in progression as measured by Erosion score and JSN score were observed following 104 weeks of treatment.

Improvement in Physical Function

As shown in Table 24, at Week 52, as well as at week 104, subjects treated with adalimumab + MTX combination therapy demonstrated greater improvement in the Disability Index of the Health Assessment Questionnaire (-1.0 units) compared to subjects treated with either MTX or adalimumab monotherapy (-0.7 for each, respectively) which was statistically significant. Similarly, and as shown in Table 25, subjects treated with adalimumab + MTX combination therapy demonstrated greater improvement in the Physical Component of SF-36 at Week 52 (16.0 units) as compared to either the MTX or the adalimumab monotherapy group (11.8, and 11.5, respectively). At Week 104, the mean improvement in the Physical Component score of the SF-36 scale was 16.1 units in the combination treatment group as opposed to 11.1 units and 11.9 units in the MTX and the adalimumab monotherapy group respectively.

Table 24. Change from Baseline in the HAQ-DI Score (Mean ± SD) at Weeks 52 and 104 (LOCF Analysis)

	MTX (N=257)	Adalimumab (N=274)	**Adalimumab + MTX (N=268)**	**p-value (a)**	p-value (b)
Baseline, n	**256**	272	**266**		
Missing data at baseline	**1**	2	**2**		
Baseline score	**1.5±0.7**	1.6±0.6	**1.5±0.6**		
LOCF subjects at Week 52, n	**252**	270	**265**		
Missing data at Week 52	**66**	83	**55**		
Change in score at Week 52	**-0.7±0.6**	-0.7±0.7	**-1.0±0.7**	**<0.001**	<0.001
LOCF subjects at Week 104, n	**252**	270	**265**		
Missing data at Week 104	**91**	112	**67**		
Change in score at Week 104	**-0.7±0.7**	-0.7±0.8	**-1.0±0.7**	**<0.001**	<0.001

(a) P-value is from the pairwise comparison of MTX monotherapy and Adalimumab + MTX combination therapy using the Wilcoxon test.

(6) P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Wilcoxon test.

Table 25. Change from Baseline in the Physical Component of SF-36 (Mean ± SD) at Weeks 52 and 104 (LOCF Analysis)

	MTX (N=257)	Adalimumab (N=274)	**Adalimumab + MTX (N=268)**	**p-value (a)**	p-value (b)
Baseline, n	**247**	264	**256**		
Missing data at baseline	**10**	10	**12**		
Baseline score	**29.6±8.2**	28.0±7.7	**29.1±8.1**		
LOCF subjects at Week 52, n	**208**	214	**232**		
Missing data at Week 52	**76**	93	**70**		
Change in score at Week 52	**11.8±9.8**	11.5±10.1	**16.0±10.3**	**<0.001**	<0.001
LOCF subjects at Week 104, n	**209**	215	**232**		
Missing data at Week 104	**97**	117	**79**		
Change in score at Week 104	**11.1±10.4**	11.9±10.1	**16.1±11.0**	**<0.001**	<0.001

(a) P-value is from the pairwise comparison of MTX monotherapy and Adalimumab + MTX combination therapy using the Wilcoxon test.
(b) P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Wilcoxon test.

6.1.4.6 Subset Analyses

As demonstrated in Tables 26 and 27, the clinical, or ACR50 response, and the radiographic response (change in modified TSS) at Week 52 was similar in different demographic subgroups. In the geriatric and in non-Caucasian subgroups the population size was too small to reach any meaningful conclusion. The apparent flattening of the treatment effect in the combination therapy group in comparison to the MTX monotherapy group in subjects weighing >85 kg, as measured by ACR50 response, was further explored by analyzing the ACR50 response in

subjects grouped by 5 kg weight increments. No weight based trend in the ACR50 response was found in the combination treatment group (data not shown).

Table26. ACR50 Response at Week 52 by Demographic Characteristics

(Non-Responder Imputation)

	MTX (N = 257)		**Adalimumab + MTX (N = 268)**	
	N	n (%)	N	n (%)
Sex				
Male	67	30 (45)	75	52 (69)
Female	190	88 (46)	193	113 (59)
Age (years)				
<40	43	19 (44)	52	37 (71)
40-64	169	80 (47)	161	98 (60)
65-74	33	15 (45)	42	22 (52)
≥75	12	4 (33)	13	8 (62)
Race				
White	242	110 (46)	250	159 (64)
Black	7	3 (43)	8	2 (25)
Asian	1	1 (100)	6	3 (50)
Other	7	4 (57)	4	1 (25)
Weight quartiles (kg)				
0 - <63	68	30 (44)	55	39 (71)
≥63 - <73	65	35 (54)	69	42 (61)
≥73 - <85.5	60	25 (42)	74	50 (68)
≥85.5 - <159	64	28 (44)	70	34 (49)

Table 27. Modified Total Sharp Score at Week 52 by Demographic Subgroups

	MTX (N = 257)			Adalimumab + MTX (N = 268)		
	N	Baseline (Mean)	Change (Mean±SD)	N	Baseline (Mean)	Change (Mean±SD)
Sex						
Male	65	21.9	7.8 ± 13.1	75	17.9	1.1 ± 3.4
Female	187	21.8	5.0 ± 12.6	193	18.2	1.4 ± 7.4
Age (years)						
<40	43	20.7	5.2 ± 15.2	52	13.8	1.7 ± 5.8
40-64	164	18.2	6.3 ± 12.2	161	16.0	1.1 ± 7.1
65-74	33	29.3	3.3 ± 13.2	42	29.4	1.4 ± 4.8
≥75	12	54.9	7.3 ± 9.7	13	25.6	2.0 ± 7.8
Race						
White	237	21.8	6.1 ± 12.4	250	18.9	1.1 ± 6.3
Black	7	28.8	-3.1 ± 26.2	8	5.5	5.1 ± 9.3
Asian	1	13.5	3.0	6	9.4	7.0 ± 11.5
Other	7	19.1	3.4 ± 4.7	4	9.1	0.6 ± 0.9
Weight (kg)						
0 - <63	67	24.1	5.3 ± 13.5	55	20.7	1.2 ± 4.2
63 - <72.4	60	23.8	6.7 ± 12.9	69	21.6	2.4 ± 6.4
72.4 - <85	60	19.9	7.2 ± 12.8	67	16.7	1.0 ± 2.8
≥85	65	19.5	4.0 ± 12.0	77	14.4	0.6 ± 9.6

Clinical (Table 28) and radiographic (Table 29) responses were further analyzed in subgroups defined by different baseline disease characteristics. It appeared that the subjects with normal CRP did not benefit from the combination therapy in either clinical or radiographic evaluation. However, the number of subjects with normal CRP (<0.5) was small, and all enrolled subjects with CRP < 1.5 had an elevated ESR (>28), therefore making this observation less relevant clinically.

Table28. ACR50 Response at Week 52 in Subgroups with Different Baseline Disease Characteristics

(Non-Responder Imputation)

	MTX (N = 257)		**Adalimumab+MTX (268)**	
	N	n (%)	N	n (%)
CRP				
Normal	18	8 (44)	32	12 (38)
Elevated	239	110 (46)	236	153 (64)
Previous DMARD use				
No	176	83 (47)	181	113 (62)
Yes	81	35 (43)	87	52 (60)
Rheumatoid factor				
Positive	215	100 (47)	228	141 (62)
Negative	41	17 (42)	40	24 (60)
Corticosteroid use				
No	166	81 (49)	172	107 (62)
Yes	91	37 (41)	96	58 (60)

N – number of subjects with a different baseline disease characteristic; n (%) – number (percent) of ACR50 responders

Table 29. Modified TSS at Week 52 in Subgroups with Different Baseline Disease Characteristics

	MTX (N = 257)			Adalimumab + MTX (N = 268)		
	N	Baseline (Mean)	Change (Mean±SD)	N	Baseline (Mean)	Change (Mean±SD)
CRP						
Normal	18	16.8	2.0 ± 7.4	32	12.0	1.9 ± 5.7
Abnormal	234	22.2	6.0 ± 13.1	236	18.9	1.2 ± 6.6
Previous DMARD use						
No	174	21.1	6.0 ± 12.8	181	17.8	1.6 ± 4.9
Yes	78	23.4	5.1 ± 12.8	87	18.7	0.8 ± 9.0
Rheumatoid factor						
Positive	212	21.6	5.4 ± 12.8	228	17.6	1.2 ± 6.8
Negative	39	23.0	7.5 ± 13.0	40	20.9	2.2 ± 4.8
Corticosteroid use						
No	164	21.9	6.1 ± 12.9	172	18.1	1.7 ± 5.2
Yes	88	21.8	5.0 ± 12.5	96	18.1	0.6 ± 8.4

The analysis of the change in the Modified TSS at Week 52 in Subgroups with Different Modified TSS at Baseline (Table 30) and the analysis of the change in the Modified TSS at Week 52 in Subgroups with Different Tender Joint Count (Table 31) showed a more significant inhibition of the radiographic progression in subjects treated with the combination therapy across the different degrees of baseline radiographic and clinical abnormalities.

Table 30. Modified TSS at Week 52 in Subgroups with Different Modified TSS at Baseline

	MTX (N = 257)			**Adalimumab + MTX (N = 268)**		
	N	Baseline (Mean)	Change (Mean±SD)	N	Baseline (Mean)	Change (Mean±SD)
TSS quartiles						
0 - <6	54	2.4	5.5 ± 10.7	66	2.7	1.6 ± 5.2
6 - <14	63	9.8	5.6 ± 12.1	71	8.9	1.6 ± 4.8
14 - <26	56	18.5	7.9 ± 11.3	73	18.9	1.5 ± 4.9
≥26	78	47.5	4.3 ± 15.4	57	46.4	0.2 ± 10.4

Table 31. Modified TSS at Week 52 in Subgroups with Different Tender Joint Count

	MTX (N = 257)			**Adalimumab + MTX (N = 268)**		
	N	Baseline (Mean)	Change (Mean±SD)	N	Baseline (Mean)	Change (Mean±SD)
TJC Quartiles						
0 - < 20	56	18.3	4.2 ± 8.8	66	22.1	2.3 ± 5.4
≥ 20 - < 30	61	24.9	2.9 ± 10.0	76	15.5	1.1 ± 9.9
≥ 30 - < 41	69	19.8	8.0 ± 13.7	61	17.7	1.0 ± 4.5
≥ 41 - < 68	66	24.1	7.3 ± 15.8	65	17.5	0.8 ± 3.5

The analysis of clinical and radiographic responses according to the financial interest and location (by continent) of investigators was consistent with a greater therapeutic effect in the combination treatment group across these subgroups, except that the number of subjects enrolled at sites with a financial interest in Abbott was too small for a meaningful assessment.

6.1.6 Efficacy Conclusion

The review of the submitted efficacy data indicates that Adalimumab + MTX combination therapy, as compared to MTX monotherapy in subjects with recently diagnosed moderate to severe RA, results in a greater improvement of signs and symptoms and inhibition of radiographic progression. Both were demonstrated to be statistically significant by the analyses of the primary endpoints: the proportion of subjects who achieved an ACR50 response and the change from Baseline in modified TSS following 52 weeks of treatment.

Following up to 104 weeks of treatment, adalimumab + MTX combination therapy, as compared to MTX monotherapy, results in greater improvement of physical function, greater improvement of signs and symptoms, greater inhibition of radiographic progression, greater achievement of a lower disease activity state, greater achievement of a major clinical response, and greater improvement in the physical components of a patient reported outcome assessment scale, with the findings being clinically and statistically significant.

The greater treatment effect of adalimumab + MTX combination therapy on clinical and radiographic response at Week 52, as compared to MTX monotherapy, is consistent across all analyzed subgroups in which a sufficient number of subjects have been included.

Review of the efficacy data from all three treatment arms indicates that, whereas improvement could be seen in each treatment arm, the greatest improvement occurred in the combination arm. Adalimumab + MTX combination therapy resulted in a greater improvement than either monotherapy in signs and symptoms, inhibition of radiographic progression, improvement in physical function, and induction of major clinical response over two years of double-blind treatment.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

As shown in Table 32, a total of six deaths occurred during the trial of HUMIRA in patients with RA of recent onset. In this as well as in the subsequent tables, the Safety Analysis Set is a term that refers to all subjects who received at least one dose of study drug.

Table 32. Subjects with Adverse Events Leading to Death (Safety Analysis Set)

Treatment Group	Sex / Age	Days on Drug at Onset	SAE Preferred Term
MTX	M / 58	25	Lobar Pneumonia NOS
Adalimumab	M / 78	476	Colon Cancer Stage IV
Adalimumab	M / 74	539	Hepatic Necrosis
Adalimumab	F / 48	611	Death NOS
Adalimumab	M / 78	50	Metastases to Liver
Adalimumab + MTX	F / 61	378	Ovarian Cancer NOS

NOS: Not Otherwise Specified

Out of five deaths that occurred in subjects receiving adalimumab, three involved malignancies of a type not unexpected in this patient population. (The topic of malignancies is discussed further below). Hepatic necrosis, listed in Adverse Reactions in the current labeling, was a cause of death in a patient with a pre-existing alcohol related liver disease. Death of "unknown cause" occurred in a 48 year old female with a history of asthma and, from the review of the narrative, appeared to have been unrelated to the study treatment.

None of the causes of mortality in this study appear to represent a new safety signal for the use of adalimumab in patients with rheumatoid arthritis.

7.1.2 Other Serious Adverse Events

Table 33 presents the overview of the treatment-emergent adverse events that have occurred during the trial of adalimumab in patients with RA of recent onset. A treatment-emergent AE is defined as any AE with onset or worsening reported by a subject from the time that the first dose of study drug was administered until five half lives (70 days) had elapsed following discontinuation of study drug administration.

Table 33. Overview of Subjects with Treatment-Emergent Adverse Events

Number (%) of Subjects with Treatment-Emergent Adverse Events (a)	**MTX (N=257)**	**Adalimumab (N = 274)**	**Adalimumab + MTX (N = 268)**
Any AE	245 (95)	262 (96)	262 (98)
AE's leading to death	1 (<1)	4 (1)	1 (<1)
Serious AE's	43 (17)	63 (23)	55 (21)
Severe AE's	49 (19)	67 (25)	68 (25)
AE's of malignancies	5 (2)	4 (2)	6 (2)
Infectious AE's	175 (68)	185 (68)	207 (77)
Serious infectious AE's	7 (3)	3 (1)	13 (5)
AE's leading to discontinuation	29 (11)	38 (14)	34 (13)

(a) Subjects may be counted in more than one AE parameter.

Except for infections, there was no difference in the number and percent of subjects who experienced AEs, serious adverse events (SAEs), malignancies, or AEs leading to death or treatment discontinuation among the three treatment arms.

As shown in Table 34, the frequency of Serious Adverse Events in the trial of HUMIRA in patients with RA of recent onset is comparable in each of the treatment arms. As illustrated in Table 35, there is no evidence of a predominant type of SAE except for arthritis-related orthopedic hospitalizations and surgical procedures which are not unusual in this patient population.

Table 34. Overview of Treatment-Emergent Serious Adverse Events

	MTX (N = 257)	**Adalimumab (N = 274)**	**Adalimumab +MTX (N = 268)**
Any SAE, number (%) of subjects	43 (17)	63 (23)	55 (21)

Table 35. Treatment-Emergent Serious Adverse Events Occurring in Two or more Subjects in Adalimumab Treatment Groups

MedDRA Preferred Term, n (%)	**MTX (N = 257)**	**Adalimumab (N = 274)**	**Adalimumab + MTX (N = 268)**
Arthralgia /Arthritis, any type	6 (2)	21 (8)	5 (2)
Cholelithiasis	0	2 (1)	3 (1)
Abdominal Pain NOS	0	1 (<1)	2 (1)
Cellulitis	0	1 (<1)	2 (1)
Pneumonia NOS	1 (<1)	0	2 (1)
Basal Cell Carcinoma	0	0	2 (1)
Angina Unstable	0	2 (1)	0
Cataract Unilateral	1 (<1)	2 (1)	0
Dehydration	1 (<1)	2 (1)	0
Thoracic Vertebral Fracture	0	2 (1)	0
Abortion Spontaneous NOS	0	2 (1)	0

7.1.2.1. Malignancies

The analysis of all treatment-emergent cases of malignancy that occurred in the trial of HUMIRA in RA of recent onset reveals a comparable frequency of malignancies among the Adalimumab and MTX containing treatment arms (see Table 36).

Table 36. Overview of Treatment-Emergent Malignancies

	MTX (N = 257)	**Adalimumab (N = 274)**	**Adalimumab +MTX (N = 268)**
All AEs of malignancies, n (%)	5 (2)	4 (2)	6 (2)

As shown in Table 37, the types of malignancy observed in this study are the types one would expect to observe in this patient population. (In addition to the treatment-emergent cases listed below, the 120-Day Safety Update contained one more case of malignancy: metastatic Squamous cell carcinoma of the lymph nodes in a 62 year old female in the adalimumab monotherapy arm).

Table 37. Subjects with Treatment-Emergent Malignancies

Treatment Group	Age/ Sex	Adverse Event	Day on Drug at Onset
MTX	43 / F	Malignant Melanoma in situ	626
MTX	59 / F	Breast Cancer NOS	116
MTX	24 / F	Lymphoma Cutis	61
MTX	78 / M	Prostate Cancer Stage I	713
MTX	64 / M	Basal Cell Carcinoma	62
Adalimumab	78 / M	Colon Cancer Stage IV	476
Adalimumab	50 / F	Breast Cancer NOS	619
Adalimumab	60 / F	Multiple Myeloma	134
Adalimumab	78 / M	Metastases to Liver	50
Adalimumab + MTX	46 / M	Basal Cell Carcinoma	417
Adalimumab + MTX	61 / F	Ovarian Cancer	378
Adalimumab + MTX	72 / M	Prostate Cancer NOS	651
Adalimumab + MTX	69 / F	Squamous Cell Carcinoma	487
Adalimumab + MTX	51 / F	Basal Cell Carcinoma	13
Adalimumab + MTX	52 / M	Basal Cell Carcinoma	93

During the review of this supplement the FDA became aware of a safety signal of malignancy in certain patients receiving the TNF blockers infliximab and etanercept. In order to further evaluate the risk of malignancy in patients treated with adalimumab, the FDA requested that the sponsor provide data on the malignancy rates in the controlled portions of all controlled adalimumab studies. This update included 5 controlled studies in RA, 2 in psoriatic arthritis, 2 in ankylosing spondylitis, and 1 each in Crohn's disease and psoriasis. The duration of studies

reported to date ranged from 4 weeks in the Crohn's disease study to 104 weeks in the RA of recent onset study. There were no malignancies reported in the studies in psoriatic arthritis, ankylosing spondylitis, or in Crohn's disease. There were 2 malignancies reported in the psoriasis study, both of which occurred in subjects who received adalimumab (one breast cancer and one squamous cell cancer). The five studies in rheumatoid arthritis involved 1922 subjects exposed to adalimumab, with median treatment duration of 5.6 months, and 947 control subjects (placebo, or MTX), with median treatment duration of 5.2 months. In these studies, there were a total of 35 malignancies reported, including non-melanoma skin cancers: 29 in subjects on adalimumab and 6 in subjects receiving control treatment. The rate of malignancies was 1.8/100-patient-years of exposure for the adalimumab group and 0.8/100- patient-years for control group. The most common malignancy reported was basal cell carcinoma (10 in the adalimumab treatment arms, and 2 in the placebo/control arms). There were 5 squamous cell carcinomas, all of which were reported by subjects in the adalimumab treated arm, yielding the total number of 15 for the non-melanoma skin cancers in the adalimumab arms, with the rate of 0.9/100-patient-years, as compared to 2 non-melanoma skin cancers in the control arms, with the corresponding rate of 0.3/100-patient-years. In a similar analysis, the rate of lymphoma was comparable between the adalimumab and the control arms, with 2 lymphomas reported in 1922 subjects in the adalimumab arms and 1 lymphoma in 947 subjects in the control arms. For the malignancies, other than lymphoma and non-melanoma skin cancer, 12 were reported in the adalimumab-treated subjects, with the rate of 0.7/100-patient-years, and 3 were reported in controls, with the rate of 0.4/100-patient-years. The types of malignancy were similar to what would be expected in the general population. It should be noted, that while the observation of an almost doubling of the rate of malignancies, other than lymphoma and non-melanoma skin cancers, in patients with RA exposed to adalimumab is clinically relevant, it did not reach statistical significance in view of the overlapping confidence intervals. The 95% CI was [0.4, 1.3] for the rate in the adalimumab treated subjects and [0.1, 1.2] for the controls. On the other hand, the control subjects (5 out of 6) were exposed to MTX monotherapy which in itself could increase the risk of malignancy.

Following an earlier agency request, the sponsor also provided an evaluation of the incidence of malignancy among patients with RA in the controlled and open-label portions of the clinical trials of Adalimumab. The analysis was conducted by the International Epidemiology Institute (IEI) looking at malignancy rates from four Abbott trials that included the trial in RA of recent onset. Combining the patients from the controlled and ongoing open-label portions of these four trials resulted in a study population of 3,042 individuals. These trials had a median duration of patient exposure of approximately three years and involved over 8500 patient years of therapy. Standardized incidence ratios (SIRs) were calculated to compare the cancer incidence in the RA patients with the cancer incidence rates of men and women in the general US population. Malignancies were grouped together under major headings used by the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) registry. The age- and sex adjusted rates obtained from SEER were used to calculate the expected incidence of each site-specific cancer. The SIR was calculated as the ratio of the observed number of cancers to the expected number of cancers for each cancer site. SIRs were calculated for the most commonly occurring cancers in the US population, as well as for any site at which more than one cancer case was observed among the 3,042 RA patients in this analysis.

Table 38. Incidence of Malignancies in 3042 Patients with RA in HUMIRA Trials

Cancer Type*	Observed	Expected	SIR	95 % CI
All Sites	80	82.76	0.97	(0.77 - 1.20)
All Lymphomas	13	3.38	3.85	(2.05 - 6.58)
Non-Hodgkin's Lymphoma	12	3.12	3.84	(1.98 - 6.72)
Hodgkin's Disease	1	0.25	3.92	(0.05 - 21.83)
Breast	13	20.23	0.64	(0.34 - 1.10)
Colon	8	8.45	0.95	(0.41 - 1.87)
Lung	5	11.63	0.43	(0.14 - 1.00)
Melanoma	4	2.82	1.42	(0.38 - 3.64)
Prostate	7	8.20	0.85	(0.34 - 1.76)
Corpus Uterus	5	4.10	1.22	(0.39 - 2.85)
Kidney	2	1.84	1.09	(0.12 - 3.93)
All other sites	23	22.12	1.04	(0.66 - 1.56)
Non-Melanoma Skin Cancer**	Observed	Expected	SIR	95 % CI
Basal Cell	44	36.37	1.21	(0.88 - 1.62)
Squamous Cell	16	6.95	2.30	(1.32 - 3.74)

* Cancer Rates from 1993-2001 SEER

** Skin Cancer rates from 1977-1978 NCI study

A total of 140 cancers were included in the SIR analysis (Table 38). Sixty were non-melanoma skin cancers and the remaining 80 included all other cancer types. For all types of malignancy taken together the SIR was 0.97 indicating no evidence of an excess of the diagnosed malignancies over what would be expected. The incidence of lymphoma is known to be elevated in patients undergoing therapy with TNF-blockers, including HUMIRA. In this study, the SIR for lymphoma was consistent with an almost 4 fold increase in the incidence of lymphoma in RA patients treated with HUMIRA as compared to the general population. Among the non-melanoma skin cancers, the SIR for basal cell carcinoma was 1.2, and was significantly elevated for Squamous cell carcinoma (SIR=2.3). It is worthwhile to note, however, that a surveillance bias and the possibility that the current skin cancer rates and the rates from over twenty years ago might not be comparable, could have led to an overestimate in the SIR for non-melanoma skin cancers. A surveillance bias might also contribute to an increased estimate of SIR for lymphoma, and the increased SIR in itself might be an overestimate of the true risks of lymphoma associated with adalimumab treatment in RA patients, as there is thought to be an increase in the "background" rate of lymphoma in patients with RA, particularly those with highly active disease.

In summary, there appears to be a new malignancy-related safety signal for the RA patients treated with adalimumab. This is supported by the accumulating evidence from the experience with some of the other TNF-blockers showing that, in addition to the risk of lymphoma, there are patient populations with an increased overall risk of malignancies with the use of these products.

The evidence is currently four fold:

1. Recent analysis of data from all controlled trials of infliximab revealed that malignancies were seen at a rate of 0.69 cases/100 pt-years compared to a rate of 0.13/100 pt-years with controls, a 5-fold higher rate.
2. In a trial of infliximab in COPD, larger numbers of malignancy cases were seen in the infliximab arm than with placebo (IND 10736).
3. In a trial of etanercept concomitantly used with cyclophosphamide or MTX in Wegener's granulomatosis, a larger number of solid tumors were observed in the etanercept arm than with control (see Enbrel® package insert).
4. There is biologic plausibility in TNF-α being an important component of the immune system and immune surveillance playing a role in preventing malignancies.

7.1.2.2. Serious Infections

In the study of adalimumab in RA of recent onset, serious infectious AEs were reported over the 2-year duration at a higher percentage in subjects receiving adalimumab + MTX combination therapy than in those receiving monotherapy with either agent. As shown in Table 39, which presents an overview of all treatment-emergent infectious adverse events including the serious ones, 5% of subjects in the combination treatment arm reported serious infectious AEs, whereas in the MTX and the adalimumab monotherapy arms serious infectious AEs were reported in 3% and 1% of subjects respectively. The 5% rate of serious infectious AEs over 2 years corresponds to 2.5 events per 100 patient-years, which is well within the range of serious infections observed in patients with untreated RA.

Table 39.Overview of Treatment-Emergent Infectious Adverse Events

n (%)	MTX (257)	Adalimumab (274)	Adalimumab + MTX (268)
Any infectious AE	175 (68)	185 (68)	207 (77)
Any serious infectious AE	7 (3)	3 (1)	13 (5)

Table 40.Subjects with Treatment-Emergent Serious Infectious Adverse Events

Treatment Group	Age / Sex	Adverse Event	Day on Drug at Onset
MTX	43 / F	Septic Arthritis NOS	577
MTX	36 / F	Sinusitis NOS	86
MTX	71 / M	Abscess NOS	493
MTX	51 / F	Pneumonia NOS	19
MTX	76 / F	Bacteremia	552
MTX	53 / F	Parotitis	288
MTX	58 / M	Lobar Pneumonia NOS	25
Adalimumab	54 / F	Lobar Pneumonia NOS	273
Adalimumab	45 / M	Cellulitis	172
Adalimumab	28 / F	Septic Arthritis NOS	580
Adalimumab + MTX	46 / M	Sinusitis Chronic NOS	469
Adalimumab + MTX	66 / M	Wound Infection NEC	682
Adalimumab + MTX	78 / F	TB Pleuritis	202
Adalimumab + MTX	47 / F	Septic Arthritis NOS	286
Adalimumab + MTX	57 / F	Lower Respiratory Infection NOS	573
Adalimumab + MTX	75 / M	Infection NOS	637
Adalimumab + MTX	59 / F	Cellulitis	311
Adalimumab + MTX	36 / F	Respiratory Tract Infection NOS	550
		Urinary Tract Infection NOS	550
Adalimumab + MTX	48 / F	Lobar Pneumonia NOS	150
Adalimumab + MTX	41 / M	Pneumonia NOS	301
Adalimumab + MTX	54 / F	Pneumonia Pneumococcal	292
Adalimumab + MTX	40 / M	Cellulitis	45
Adalimumab + MTX	75 / F	Pneumonia NOS	160

As shown in Table 40, the types of serious infectious AEs reported in this clinical trial were comparable across three treatment arms, with the most frequent ones being pneumonia, cellulitis and septic arthritis. All were treated with antibiotics, and there were no deaths. The case of TB Pleuritis occurring with the combination treatment is discussed further in the section on Tuberculosis. The two additional cases of active TB, including one with a fatal outcome from surgical complications, were not initially reported as treatment-emergent SAEs but are also discussed in the TB section. In reference to serious infections other than TB, the data obtained in this study do not appear to represent a new safety signal.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As illustrated in Table 41, the overall rate of study drug discontinuation due to an adverse event is comparable across three treatment arms.

Table 41. Overview of Treatment Emergent Adverse Events Leading to Premature Discontinuation of Study Drug

	MTX (257)	Adalimumab (274)	Adalimumab + MTX (268)
Total Subjects, n (%)	29 (11)	38 (14)	34 (13)

7.1.3.2 Adverse events associated with dropouts

Table 42 lists diagnostic categories grouping the adverse events that resulted in study drug discontinuation. The category of abnormal LFTs, a known cause of discontinuation of a MTX containing therapy, is discussed further in the section on Laboratory abnormalities. (b) (4)

Table 42. Treatment-Emergent Adverse Events Resulting in Study Drug Discontinuation

Diagnostic Categories n (%)	MTX (257)	Adalimumab (274)	Adalimumab + MTX (268)
Abnormal LFTs	4 (2)	2 (1)	9 (4)
Infections	1 (<1)	7 (3)	6 (2)
Respiratory Disorders	1 (<1)	3 (1)	5 (2)
Nervous System Disorders	0 (0)	4 (2)	3 (1)
Musculoskeletal Disorders	7 (3)	14 (5)	2 (1)
Neoplasms	3 (1)	4 (2)	2 (1)
Neutropenia	0 (0)	0 (0)	2 (1)

* Listed diagnostic categories occurred in two or more subjects in the combination treatment group

7.1.3.3 Other significant adverse events

7.1.3.3.1 Tuberculosis

In the trial of adalimumab in RA of recent onset subjects were screened for latent TB infection with chest X-ray (CXR), tuberculin skin test (PPD), or both, depending on the country of study site location. The cut-off for a positive PPD reaction varies from country to country but usually consists of 5 mm (e.g. Germany) or 10 mm (e.g. France) in induration. A CXR was used to screen for TB in Europe, and a PPD and CXR were used in North America. As a result of the screening, 30 subjects received TB prophylaxis. All were screened by CXR and 20 were screened by both CXR and PPD. Nineteen subjects were from the US and eleven were from Europe. Eleven subjects were positive for latent TB by tuberculin skin test and 17 had CXRs indicative of latent TB. There were 7 subjects who started their prophylaxis between 1 and 25 days prior to receiving adalimumab. All other subjects started their TB prophylaxis on the day they started their study treatment. Of the 30 patients receiving TB prophylaxis, only a single US patient (see below) developed active TB during or after the treatment with Adalimumab. Three subjects, all in the adalimumab + MTX treatment group, developed tuberculosis (TB) during their participation in the study. Two were from Europe and were screened with chest X-rays only. Both subjects had a normal CXR and no prophylaxis was given. One developed pleural TB at 26 weeks, was taken off the study medication, and treated successfully. The other subject, after completing the 104 weeks of the study medication, had a right hemicolectomy for what was interpreted as a tubercular lesion and, after a protracted hospital course, died of surgical complications. TB in the latter case was diagnosed on the basis of a biopsy showing necrotizing granulomas, although no organisms were identified. The third subject was from the US, had a history of previously treated TB, had an 80 mm positive skin test at screening and a negative CXR, and was given 6 month INH prophylaxis at the start of the adalimumab + MTX therapy, but 3 years later, while on open-label extension, developed miliary TB, which was treated successfully while the study medication since then had been discontinued.

According to Abbott, through 12-31-2004 there were 13,081 subjects treated with Adalimumab in the clinical trials worldwide, the vast majority involving rheumatoid arthritis. This includes 4718 subjects from trials conducted in US and Canada, 7979 subjects from trials in Europe and Australia, and the remainder from Latin America and Asia. In terms of patient-years of exposure, these figures can be translated into (b) (4) patient-years in US/Canada and (b) (4) patient-years in Europe/Australia. The incidence of TB in the general population varies from 5 per 100,000 in US and Canada, to 10 to 40 in Western Europe, to approximately 100 in Eastern Europe and India, and higher in other parts of the world. Screening for TB in the Adalimumab protocols began in '99, about a year and a half after the initiation of the clinical development program. There were a total of 42 cases of TB identified in the search of the safety database of clinical trials through 12-31-04, of which eight occurred prior to the initiation of screening. All were receiving Adalimumab for RA, and all but four were on concomitant corticosteroid therapy and/or DMARDS. The mean age was 60 years and 76% were females, reflecting the population of the studies. A positive MTB culture was obtained in 62%. Extrapulmonary disease was present in 26

cases (62%). The mean time to diagnosis of TB was 10 months, and the median time to diagnosis was 7 months (range: 1 to 54 months). There was one case of TB reactivation, mentioned above, that occurred after the completion of the adalimumab therapy. Five cases were from US and Canada, two from Mexico, five from Asia, and 30 were from Europe. There were two TB related fatalities, both in Europe.

The calculation of the overall global rate of cases yields 0.26 events per 100 patient/years of exposure. For US and Canada the rate is 0.07 cases/100 patient-years. The rate for Europe is five times higher which is consistent with the previously cited statistics of the incidence of TB in Europe as compared to US. The rate of cases has not changed over time in either Europe or US. With five cases of TB occurring in 4718 US patients exposed to Adalimumab, the incidence rate can be calculated as 0.106%. This incidence rate should be interpreted with caution, given the heterogeneity of US population, especially of its immigrant component.

Whereas screening appears to have resulted in 85% reduction in the incidence of TB, the effectiveness of INH prophylaxis was further assessed in a European study of 6610 subjects with RA receiving Adalimumab. TB screening involved a chest X-ray and a PPD which was read in accordance with the local standards. The screening identified a total of 712 subjects who, as a result, received INH prophylaxis. Four subjects in that study developed TB in spite of INH prophylaxis.

Currently available data suggest that, as with some of the other TNF blockers, treatment with adalimumab predisposes to reactivation of the latent TB, and that in vast majority, patients who receive prophylactic anti-TB treatment can be safely treated with adalimumab. However, the optimal duration and time of initiation of anti-TB prophylaxis in relation to treatment with adalimumab is unknown.

7.1.3.3.2 Opportunistic Infections

No cases of histoplasmosis, aspergillosis, pneumocystis, listeria, systemic candidiasis, coccidioimycosis, or blastomycosis were reported in the trial of adalimumab in RA of recent onset.

In the database of 13,081 subjects treated in clinical trials with adalimumab worldwide, a total of 12 cases out of 16,107 patient-years have been reported, which amounts to the rate of 0.075 events per 100 patient-years. There was no predominant type of infection. These included 4 cases of Histoplasmosis, with one fatality, one case of Aspergillosis which was fatal, and one case of Listeriosis complicated by fatal ARDS. There were two cases of Nocardiosis, two cases of Candidiasis, one case of Cryptococcus, and one case of Pneumocystis, which were all non-fatal, having responded to the appropriate therapy.

7.1.3.3.3 Other Infections

In the study of adalimumab in RA of recent onset, the most frequent infection encountered was nasopharyngitis affecting 31% of subjects in the Adalimumab+MTX combination treatment group, 22% in the Adalimumab monotherapy group, and 25% in the MTX monotherapy group. The other frequently reported infections were upper respiratory infections, pharyngitis, and sinusitis, all occurring at comparable frequencies across the treatment groups. The study was notable for an 8% occurrence rate of Herpes Simplex in the combination treatment group, which is discussed in the following section.

7.1.3.3.4 Herpes Simplex and Herpes Zoster Infections

As shown in Table 43, more subjects in the Adalimumab+MTX combination group developed Herpes Simplex than in either monotherapy group.

Table 43. Treatment-Emergent Infections with Herpes Simplex Virus

	MTX (N=257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Number of subjects/ known past history	12 / 4	10/ 1	23 / 3

There were a total of 45 subjects with at least one episode of Herpes simplex infection throughout the study. None of these episodes were SAEs and no subject withdrew from the study with a primary reason of herpes simplex. There were no cases reported of serious herpes infection manifestations such as aseptic meningitis, disseminated disease, encephalitis, or visceral infections. All of the infections were oral-facial in location. One subject in the adalimumab monotherapy group had an additional genital herpes episode as well.

There were 14 cases of herpes zoster (shingles) reported in the study: 2 cases in the MTX monotherapy group, 8 in the adalimumab monotherapy group, and 4 in the adalimumab + MTX combination therapy group. None of these cases were SAEs and disseminated disease was not reported for any of these cases. One subject in the adalimumab monotherapy group withdrew from treatment due to herpes zoster while no subjects in the MTX monotherapy group or the Adalimumab+MTX combination therapy group withdrew from treatment due to this AE.

Overall, these viral infections do not appear to represent a new safety signal for use of adalimumab in rheumatoid arthritis.

7.1.3.3.5 Demyelinating Disorders

Demyelinating Disorders are listed in the Warnings section of the HUMIRA label. To update these data, the adverse drug event database was searched for all clinical trial, post-marketing, and literature reports. Eleven reports were received. Two reports described either pre-existing symptoms or a pre-treatment MRI abnormality, and nine described initial neurological symptoms or an abnormal MRI. None of the nine reports provided baseline exam or MRI. Where the outcome was provided, six patients recovered. No demyelinating events were reported in the trial of adalimumab in RA of recent onset.

7.1.3.3.6 Lupus-like Reactions

Lupus-like Reactions are listed in the Warnings section of the HUMIRA label. One case of a lupus-like reaction was reported by a subject receiving adalimumab monotherapy in the study of adalimumab in RA of recent onset. The event occurred in a 35-year old female following 269 days of study treatment. It was of moderate severity, and was manifested by positive ANA, lymphopenia and "extra-articular inflammation'. The patient improved following discontinuation of therapy.

7.1.3.3.7 Congestive Heart Failure

Congestive Heart Failure is listed in the (b) (4) section of the HUMIRA label. Two subjects were reported to have developed heart failure as an SAE, one in each of the monotherapy arms.

7.1.7 Laboratory Findings

In the trial of HUMIRA in patients with RA of recent onset, no new safety signals in relation to the laboratory assessment were identified. Analyses of mean changes in the individual laboratory parameters, including Hematology, Clinical Chemistry, and Coagulation, from baseline to Week 104, did not reveal any clinically important differences between the treatment arms. The analysis of the proportion of subjects who shifted from normal/negative laboratory values in Hematology, Clinical Chemistry, Coagulation, and ANA titers, at baseline to abnormal/positive values at the final visit, likewise, did not show clinically significant differences between the treatment arms. The number of subjects with laboratory abnormalities of toxicity Grade 2 or higher at either Baseline or Weeks 52 or 104 was small; no differences among treatment groups were apparent. In addition, no clinically significant or relevant differences between treatment groups were found when the numbers and percentages of subjects with Grade ≥ 2 laboratory abnormalities that occurred at anytime from Baseline to Week 52 were compared. Just two Grade 4 events occurred during the study: hyperuricemia (adalimumab monotherapy) and hyperglycemia (in a known

diabetic on adalimumab + MTX combination therapy), neither one presenting with clinical manifestations or resulting in study treatment discontinuation.

The issue of Liver Function Test abnormalities found during the HUMIRA trial in patients with RA of recent onset was specifically addressed by further examining data from subjects with Grade $\geq$ 3 ALT elevations and subjects who discontinued due to the LFT abnormalities in either of the adalimumab containing treatment arms. Elevated levels of serum aminotransferases have been reported in patients with RA who have not received systemic pharmacologic therapy, and the interpretation of the LFT abnormalities in the combination treatment arm is further confounded by the fact that all patients enrolled in the study were MTX naïve, with the pattern of the abnormalities, when present, being consistent with the one also seen with MTX that is well known for its hepatotoxicity. Out of six subjects with Grade 3 ALT elevations (there were no Grade 4 elevations) in the adalimumab containing treatment arms, five were receiving combination therapy and one was receiving adalimumab monotherapy. The one subject in the adalimumab monotherapy arm had a single recorded ALT elevation to five times the upper limit of normal which resolved on adalimumab. Five subjects with Grade 3 ALT elevations in the combination treatment arm discontinued study treatment. In four of them, ALT normalized, and in the other one the ALT elevation was associated with the initiation of anti-TB therapy and resolved with a change in that therapy. In addition to five subjects with Grade 3 ALT elevation, there were four subjects with Grade 2 ALT elevation, for a total of nine in the combination treatment arm who discontinued due to an LFT abnormality. All these LFT abnormalities also resolved upon the discontinuation of the study treatment. In the adalimumab monotherapy arm, there were two subjects, both with Grade 2 ALT elevation, who discontinued study treatment. One subject was lost for follow-up, in the other the LFTs normalized off treatment. No pattern was detected in respect to timing of development of LFT abnormalities; there was no evidence of associated hyperbilirubinemia, and no hepatobiliary AEs were reported in any of these subjects.

7.1.17 Postmarketing Experience

7.1.17.1 Interstitial Lung Disease

As a follow-up to the one-year postmarketing safety review of adalimumab submitted by ODS on July 13, 2004, and based on the review of the ODS data that as of May 11, 2005 included 9292 adverse event reports in the AERS database, an additional consultation was requested to assess the cases of Interstitial Lung Disease (ILD) occurring in patients treated with adalimumab. Reference is made to the report (PID#: D050276) submitted by Hyon J. Kwon, safety evaluator from the Division of Drug Risk Evaluation, on August 16, 2005.

Out of 9292 adverse event reports, an additional AERS search identified 115 potential lung injury cases reported with adalimumab use of which fourteen cases without other potential etiologies for ILD were further reviewed. Except for two patients who did not specify the indication for use, all patients received adalimumab for the treatment of rheumatoid arthritis. The patients' ages ranged from 49 to 85 years with a median of 71 years. Most (9/14) cases

occurred in females. Dyspnea (6) and/or dry cough (2) were common presentations in these patients. Reported adverse events included pulmonary fibrosis (7), interstitial pneumonia (4), and alveolitis (3). All cases showed a temporal association between the drug exposure and the development of lung injury; the time to onset of a pulmonary event ranged from 1.5 to 11 months, with a median of 6 months. Although patients with pre-existing ILD were excluded, the analysis of the data was confounded by the known occurrence of interstitial lung disease as a pulmonary manifestation of RA. Seven cases were also confounded by concomitant therapy with methotrexate (MTX), leflunomide, and/or sulfasalazine, which are drugs that have been associated with and labeled for ILD. Two patients reported regression of lung disease after discontinuation of adalimumab and treatment with corticosteroids. Five patients with pulmonary fibrosis did not respond to drug withdrawal. Eight of 14 cases resulted in hospitalization. A fatal outcome was reported in four patients. The cause of death was ILD in two patients who died despite adalimumab withdrawal and corticosteroid therapy. The other two deaths occurred in patients who discontinued MTX but continued adalimumab therapy.

The current adalimumab labeling does not mention interstitial lung disease. Whereas underreporting is a well-recognized limitation of the post-marketing database, it could be even more significant for ILD in patients with RA because it is a known complication of RA. Of further concern is the serious nature of the outcomes reported in the ODS consult. This reviewer therefore recommends that the post-marketing adverse reaction section of the HUMIRA labeling be updated to indicate that interstitial lung diseases, including pulmonary fibrosis, have been observed with adalimumab.

7.1.17.2 Hepatic Events

In relation to hepatic events, adalimumab is labeled for "hepatic necrosis" in the Adverse Reactions section. The ODS one-year postmarketing adalimumab safety review of July 13, 2004 did not find any serious, unlabeled hepatic adverse events. The September 21, 2004 ODS report entitled "Severe Hepatotoxicity and Liver Failure cases with infliximab, etanercept, and adalimumab" did not recommend further changes to the adalimumab label.

In response to the FDA request, Abbott submitted a postmarketing report with the analysis of all spontaneous reports of hepatic events coincident with adalimumab therapy and included it with the efficacy supplement on the use of adalimumab in patients with RA of recent onset. The adalimumab safety database was searched for all postmarketing and literature reports received between 12-31-02 and 9-30-04. The identified cases were subdivided into two groups. The first group contained reports of cases with MedDRA v7.0 Preferred Terms describing hepatic events limited to the Investigations System of Classification (SOC). Reports in this group most commonly described varying degrees of elevation of hepatic enzymes as the hepatic event. The review of these cases showed that they were associated with use of concomitant hepatotoxic medications or occurred in the setting of other acute illness. No clear causal relationship to adalimumab therapy was identified.

The second group contained the reports with Preferred Terms describing hepatic events from other SOCs including the Hepatobiliary SOC. There were 19 such reports. The report sources were consumer sources in 4 reports (21%) and were confirmed by health care professionals in 15 reports (79%). Twelve (63%) of the 19 reports were considered serious from a regulatory perspective. The demographic characteristics of the reports were consistent with the typical RA patient population. Five (26%) of the 19 reports described male patients and 13 (68%) described female patients. The age of the patients ranged from 32 to 76 years with a median age of 56 years. Fourteen of the reports originated from the U.S. The time to onset of the event ranged from 14 to 128 days with a median of 30 days.

Three out of 19 reports carried the diagnosis of hepatitis C. Four reports described a non-specific liver disorder, which could be interpreted as drug- or alcohol-induced, but no details were provided. There were three reports of jaundice, two of which contained no laboratory data, and one was in a setting of surgical complications of a ruptured aortic aneurism. Six cases, which included two terms of hepatic failure, two terms of hepatitis, and one case each of hepatic necrosis and hepatic steatosis, occurred in a setting of disseminated infection and/or multi-organ failure. The remaining three cases were termed as hepatitis based on the presence of mild LFT abnormalities. No additional information on any of these cases is available in spite of several queries, according to the sponsor.

Overall, the available data in the reports of hepatic events coincident with adalimumab treatment appear to indicate that the events are consistent with those expected in the RA population reflecting the presence of underlying disease, coincidental acute morbidities, or toxicities of concomitant medications. These reports do not indicate a causal relationship between adalimumab treatment and the reported events, and no labeling changes will be recommended at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

All 799 subjects who received at least 1 dose of study drug were accounted for in the safety summaries and analyses through the end of the study regardless of whether they had discontinued study treatment. Extent of exposure is shown in Table 44.

Table 44. Extent of Exposure and Cumulative Exposure (Safety Analysis Set)*

	MTX	Adalimumab	Adalimumab + MTX
Duration of Treatment (days)			
Number of Subjects	257	274	268
Mean ± SD	575.2 ± 244.6	545.1 ± 258.4	621.7 ± 216.2
Median	728.0	727.0	729.0
Range (min-max)	1.0 – 773.0	1.0 – 749.0	1.0 – 807.0
Adalimumab Exposure, n (%)			
≤ 4 weeks	N/A	274 (100)	268 (100)
>4 weeks	N/A	271 (98.9)	264 (98.5)
>12 weeks	N/A	256 (93.4)	257 (95.9)
>26 weeks	N/A	225 (82.1)	244 (91.0)
>52 weeks	N/A	195 (71.2)	221 (82.5)
>76 weeks	N/A	179 (65.3)	213 (79.5)
≥104 weeks	N/A	135 (49.3)	174 (64.9)

* **The safety analysis set**: all subjects who received at least one dose of study drug

The median duration of treatment for each of the study groups was greater than 727 days, consistent with the duration of the study (104 weeks, or 728 days). In reference to the overall adalimumab exposure, all subjects randomized to either the combination therapy group or the adalimumab monotherapy group received adalimumab for at least four weeks. Longer durations of exposure to adalimumab were seen in those subjects treated with adalimumab + MTX combination therapy than in those subjects treated with adalimumab monotherapy.
The type and the number of safety assessments performed in this study appear to be adequate; and the extent of exposure to adalimumab in this study's population appears to have been sufficient for the evaluation of safety of adalimumab in patients with RA of early onset.

9. OVERALL ASSESSMENT

9.1 Conclusions

Given the substantial benefit (see Efficacy Conclusions, section 6.1.6) of improvement in signs and symptoms, inhibition of radiographic progression, improvement of physical function, induction of major clinical response, the overall high rate of low disease activity achieved in subjects recently diagnosed with moderate to severe RA, and given the acceptable safety profile, the benefit to risk ratio for treatment with adalimumab appears to be positive and justifies extension of the indication for adalimumab to also include recently diagnosed MTX-naïve patients with moderately to severely active Rheumatoid Arthritis. There was a substantially greater treatment effect achieved with the adalimumab therapy in combination with MTX than with adalimumab monotherapy.

In the review of the Efficacy Supplement, no new safety signals were identified with adalimumab + MTX combination therapy or adalimumab monotherapy, and in general, the benefits of adalimumab treatment outweighed the potential risks in subjects with RA of recent onset treated for two years. The safety concerns that have arisen as a result of the review of the Labeling Supplement, including but not limited to data on TB and malignancies, should be addressed in the revisions to the current labeling.

9.2 Recommendation on Regulatory Action

The reviewer recommends approving the BLA efficacy supplement STN#: 125057/46 for the use of adalimumab at the recommended doses in patients with moderate to severely active RA with modifications to the proposed labeling.

9.3 Recommendation on Postmarketing Actions

Based on the review of the efficacy supplement, no new postmarketing studies should be required as no new safety signals were identified in this trial and no new questions regarding lack of efficacy have been raised.

10 APPENDIX

Handling Rules for Missing TSS Data at Baseline or Week 52 (similar rules at week 104).

1. If a subject had TSS at Baseline and Week 26 but the Week 52 TSS was missing, the Week 52 TSS was imputed by linear extrapolation using the Baseline and Week 26 TSS.
2. If a subject had TSS at Baseline but the Week 52 TSS and Week 26 TSS were missing, the Week 52 TSS was imputed by linear extrapolation using the Baseline and TSS evaluated at early termination.
3. If a subject has TSS at Baseline but no follow-up TSS prior to and including Week 52, the Week 52 TSS was imputed using the 75th percentile of non-missing Week 52 TSS based on the adalimumab + MTX combination therapy group and the MTX monotherapy group combined.
4. If a subject had TSS at Week 52 but no TSS at Baseline, the Baseline TSS was imputed using the median of non-missing Baseline TSS based on the adalimumab + MTX combination therapy group and the MTX monotherapy group combined.
5. If TSS was missing at both Baseline and Week 52, the TSS change from Baseline at Week 52 was imputed using the 75th percentile worsening of non-missing TSS change from Baseline at Week 52 based on the adalimumab + MTX combination therapy group and the MTX monotherapy group combined.

Appendix Table

	MTX (N=257)	Adalimumab (N=274)	Adalimumab + MTX (N=268)
Number of Subjects with a Single Set of X-rays			
Baseline	13	16	9
Early Termination	1	0	0
Number of Subjects with No X-rays	4	3	0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BL 125057/46
Drug Name:	HUMIRA® (adalimumab)
Indication(s):	Treatment of early stage of rheumatoid arthritis (RA)
Applicant:	Abbott Laboratories
Date(s):	Received date: 12/24/04; Action Date: 09/30/05
Review Priority:	Standard
Biometrics Division:	Biologics Therapeutics Statistical Staff
Statistical Reviewer:	Kyung Yul Lee, Ph.D.
Concurring Reviewers:	Boguang Zhen, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	DTBIMP
Clinical Team:	Alex Gorovets, MD
Project Manager:	Erik Laughner

Keywords: Adalimumab, Methotrexate (MTX)-naive, Rheumatoid Arthritis, Randomized trial

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1. EXECUTIVE SUMMARY

BLA supplement 125057/46 is an extension of the submission on adalimumab (HUMIRA®) for the treatment of moderately to severely active rheumatoid arthritis (RA) patients who have had an inadequate response to other disease modifying antirheumatic drugs (DMARDs). Results from Study DE013 were included in this supplement.

Study DE013 was designed to primarily assess the effectiveness of adalimumab + MTX combination therapy over MTX monotherapy in reducing signs and symptoms of disease and inhibiting joint destruction in subjects with recent-onset RA (disease duration < 3 years) not previously treated with MTX.

1.1 Conclusions and Recommendations

In DE013 study, there is a statistically significant difference in favor of adalimumab + MTX combination treatment compared with MTX monotherapy for the proportion of subjects with an ACR50 response at Week 52 (see Table 2) which is the primary analysis in improving on signs and symptoms and the change from baseline in modified TSS at Week 52 (see Table 3) which is the co-primary analysis in inhibiting radiographic progression.

This study supports the effectiveness of adalimumab 40 mg eow + MTX ≤ 20 mg/week combination treatment in the reduction in signs and symptoms and in inhibition of the progression of structural damage in subjects with recent-onset RA (disease duration < 3 years) not previously treated with MTX.

1.2 Brief Overview of Clinical Studies

Adalimumub (HUMIRA®) is currently approved to treat adult subjects with moderately to severely active RA who have had an inadequate response to other disease modifying antirheumatic drugs (DMARDs).

1.2.1 Study Design

Study DE013 is a double-blind active-comparator two year study to primarily assess the potential of adalimumab + MTX combination therapy in improving signs and symptoms of disease and inhibiting joint destruction in subjects with recent-onset RA (disease duration < 3 years) not previously treated with MTX.

1.2.2 Patients Disposition

The full analysis set, the primary analysis population for Study DE013, included all subjects who were randomized and who received at least one dose of double blinded study medication.

A total of 799 subjects were randomized in a 1:1:1 ratio to receive a combination of adalimumab 40 mg eow + MTX (≤ 20 mg/week, n=264), adalimumab 40 mg eow monotherapy (n=274), or MTX monotherapy (≤ 20 mg/week, n=257) for two years. The following Table 1 shows the number of patients at randomization, completed, and discontinued including discontinued due to lack of efficacy and adverse events among the total of 799 subjects with moderately to severely active recent-onset RA.

Table 1. Number of patients randomized and discontinued by treatment.

	MTX n,(%)	Adalimumab n,(%)	Adalimumab+MTX n,(%)	Total
Randomized	257	274	268	799
Week 52				
Completed	196(76.3)	194(70.8)	220(82.1)	610(76.3)
Discontinued	61(23.7)	80(29.2)	48(17.9)	189(23.7)
Lack of efficacy	32(12.5)	43(15.7)	12(4.5)	87(10.9)
Adverse event	14(5.4)	19(6.9)	22(8.2)	55(6.9)
Week 104				
Completed	169(65.8)	167(60.9)	203(75.7)	539(67.5)
Discontinued	88(34.2)	107(39.1)	65(24.3)	260(32.5)
Lack of efficacy	46(17.9)	52(19.0)	13(4.9)	111(13.9)
Adverse event	19(7.4)	26(9.5)	32(11.9)	77(9.6)

All randomized patients received at least one dose of double blinded medication. The subjects who completed the 2-year double-blind period were MTX 65.8%; adalimumab 60.9%; and adalimumab + MTX 75.7%. A total of 32 (11.9%) subjects in the adalimumab + MTX combination therapy group, 26 (9.5%) subjects in the adalimumab monotherapy group, and 19 (7.4%) subjects in the MTX monotherapy group withdrew due to an adverse event (AE) as a primary reason. Of the subjects who completed the 2-year double-blind period of the study, only 13 (4.9%) subjects in the adalimumab + MTX combination group withdrew due to lack of efficacy as a primary reason compared to 52 (19.0%) subjects in the adalimumab monotherapy group and 46 (17.9%) subjects in the MTX monotherapy group. Subject disposition at Week 52 was comparable to that of Week 104.

1.2.3 Efficacy Endpoints

There were two co-primary efficacy endpoints in Study DE013. The first primary efficacy endpoint, the proportion of subjects with an ACR50 response at Week 52, was used to demonstrate the superiority of adalimumab + MTX combination therapy vs. MTX monotherapy in improving signs and symptoms. The second primary efficacy endpoint was the change from Baseline in modified TSS at Week 52 to demonstrate the superiority of adalimumab + MTX combination therapy vs. MTX monotherapy in inhibiting radiographic progression.

The statistical tests were performed in a hierarchical manner to protect type I error. First, the primary analysis on signs and symptoms as described in the statistical analysis plan was statistically significantly different in favor of adalimumab + MTX combination treatment compared with MTX monotherapy, so the second primary analysis of inhibition of radiographic progression was performed. Otherwise, the analysis of inhibition of radiographic progression was to be considered as a secondary analysis.

Major secondary efficacy endpoints, which were pre-specified to demonstrate the positive effect of adalimumab + MTX combination therapy in improvement of physical function, improvement of signs and symptoms, inhibition of radiographic progression, achievement of clinical remission as defined by DAS28 < 2.6, improvement in quality of life (QoL) in terms of the physical component of SF-36, and achievement of a major clinical response defined as an ACR70 response for six continuous months.

1.3 Statistical Issues and Findings

1.3.1 Sponsor's Analyses

Pearson's χ^2 test was used for analysis of the first primary efficacy endpoint of the proportion of ACR50 responses using full analysis set. Two sensitivity analyses were performed using all data as observed without imputation for missing data (considered as non-responders) and the last observation carried forward (LOCF) approach for ACR50 response.

The Mann Whitney test was used for the analysis of the second primary efficacy endpoint of the change from baseline in modified TSS with full analysis. Missing values for TSS were imputed by a pre-defined linear progression method. Sensitivity analyses were also performed to assess the robustness of the co-primary statistical analysis of change from baseline in modified TSS at Week 52. These sensitivity analyses included using LOCF methods, observed values, an ANOVA model, and 75th percentile.

Table 2 summarizes the sponsor's results of efficacy endpoints, ACR20, ACR50 and ACR70 responses and major clinical response, defined as the subjects achieving and maintaining an ACR70 response for 6 continuous months over 104 weeks of treatment.

Table 2. ACR20/50/70 and Major Clinical Responses at Weeks 52 and 104 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)		
	n (%)	n (%)	n (%)	p-value[a]	p-value[b]
ACR20					
Week 52	161 (62.6)	149 (54.4)	195 (72.8)	0.013	<0.001
Week 104	144 (56.0)	135 (49.3)	186 (69.4)	0.002	<0.001
ACR50					
Week 52	118 (45.9)	113 (41.2)	165 (61.6)	<0.001	<0.001
Week 104	110 (42.8)	101 (36.9)	158 (59.0)	<0.001	<0.001
ACR70					
Week 52	70 (27.2)	71 (25.9)	122 (45.5)	<0.001	<0.001
Week 104	73 (28.4)	77 (28.1)	125 (46.6)	<0.001	<0.001
Major Clinical Response[c]					
Week 104	70 (27.2)	67 (24.5)	130 (48.5)	<0.001	<0.001

Note: Subjects with missing values were counted as non-responders.
a. P-value is from Pearson's chi-square test of MTX monotherapy vs adalimumab + MTX combination.
b. P-value is from Pearson's chi-square test of adalimumab monotherapy vs adalimumab + MTX combination.
c. Subjects achieving and maintaining an ACR70 response for 6 continuous months

The primary endpoint of ACR50 at Weeks 52 shows statistically higher responses in the adalimumab + MTX combination therapy group compared to the MTX and adalimumab monotherapy groups. For the secondary endpoints of ACR20 and ACR70 at weeks 52 and 104 and ACR50 at week 104, the results show consistent pattern with that of ACR50. Following 104 weeks of treatment, 48.5% (130/268) of subjects who received adalimumab + MTX combination therapy and 24.5% (67/274) of subjects who received adalimumab therapy achieved a major clinical response compared to 27.2% (70/257) of subjects who received MTX monotherapy ($p<0.001$).

The co-primary endpoint of the change from baseline in modified TSS at week 52 can be tested because the first primary endpoint of ACR50 response of adalimumab +MTX group was statistically significantly higher ($p<0.0001$) than MTX and adalimumab monotherapy groups. Table 3 presents the summary of the sponsor's results on the change from baseline in modified TSS at week 52.

Table 3. Change in Modified Total Sharp Score from Baseline at Weeks 52 and 104 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[a]	p-value[b]
Week 52					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 52 (mean)	27.6 ± 24.6	21.8 ± 19.7	19.4 ± 19.9		
Change at Week 52 (mean ± SD)	5.7 ± 12.7	**3.0** ± 11.2	**1.3** ± 6.5	<0.001	0.002
Week 104					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 104 (mean)	32.3 ± 30.0	24.3 ± 23.2	20.0 ± 20.5		
Change at Week 104 (mean ± SD)	**10.4** ± 21.7	**5.5** ± 15.8	**1.9** ± 8.3	<0.001	<0.001

Note: An increase in modified TSS is indicative of disease progression and/or joint worsening. In contrast, no change in modified TSS represents a halting of disease progression and a decrease represents improvement.
Note: Primary analysis imputation used for missing data.
a. P-value is from the Mann-Whitney U test of MTX monotherapy vs. adalimumab + MTX.
b. P-value is from the Mann-Whitney U test of adalimumab monotherapy vs. adalimumab + MTX.

Subjects treated with adalimumab + MTX combination therapy had a statistically low mean increase of **1.3** Sharp units compared to **5.7** Sharp units in subjects treated with MTX monotherapy ($p<0.001$) for change from baseline of modified TSS at week 52. For the secondary endpoints of change from baseline in modified TSS at week 104, the results were consistent to that of week 52.

A summary of the number (%) of subjects with no worsening (defined as change from Baseline of ≤ 0.5 in the modified TSS and erosion and JSN scores) at Weeks 52 and 104 is presented in Table 4.

Table 4. Subjects With No Worsening in Modified TSS and Components from Baseline at Weeks 52 and 104 (All Randomized Subjects)[a]

	MTX (N = 257)		Adalimumab (N = 274)		Adalimumab + MTX (N = 268)			
	N	n (%)	N	n (%)	N	n (%)	p-value[b]	p-value[c]
Modified TSS								
Week 52	257	96 (37.4)	274	139 (**50.7**)	268	171 (**63.8**)	<0.001	0.002
Week 104	257	86 (33.5)	274	122 (**44.5**)	268	164 (**61.2**)	<0.001	<0.001
Erosion score								
Week 52	257	111 (43.2)	274	165 (60.2)	268	190 (70.9)	<0.001	0.009
Week 104	257	104 (40.5)	274	143 (52.2)	268	184 (68.7)	<0.001	<0.001
JSN score								
Week 52	257	145 (56.4)	274	174 (63.5)	268	208 (77.6)	<0.001	<0.001
Week 104	257	123 (47.9)	274	166 (60.6)	268	194 (72.4)	<0.001	0.004

JSN: joint space narrowing
Note: Primary analysis imputation was used for missing data.
a. No worsening defined as change from Baseline of ≤ 0.5.
b. P-value is from the Pearson's chi-square test of MTX vs. adalimumab + MTX.
c. P-value is from the Pearson's chi-square test of adalimumab vs. adalimumab + MTX.

During 52 and 104 weeks of treatment, a significantly greater proportion of subjects who received adalimumab + MTX combination therapy showed no worsening in modified TSS (defined by a change from Baseline of ≤ 0.5) compared to subjects who received adalimumab monotherapy and MTX monotherapy. The MTX monotherapy group had the numerically lowest proportion, the adalimumab monotherapy group had a higher proportion, and the adalimumab + MTX combination group had the highest proportion of subjects with no worsening in modified TSS as seen change in modified TSS from baseline analysis. For erosion score and JSN score, similar trends at Weeks 52 and 104 were observed in the components of the modified TSS.

1.3.2 Reviewer's Analysis

The reviewer used the partial imputation method as sensitivity analyses for the co-primary efficacy endpoints by partially imputing the missing data with LOCF to create the similar drop-out rates among three treatment groups, so that the sample distribution of the follow-up time in the three arms become equal and dependence between response variable and the drop-out process in the three groups are equal (Lynn Wei and Weichung J. Shiu, 2001). This partial imputation approach may be better for the estimation or test of the treatment difference than the LOCF or all available data analyses because this approach provides unbiased estimation of the treatment effects and empirical coverage of the 95% confidence intervals very close to the normal level.

As an alternative to the sponsor's primary analysis of ACR50 response at Week 52, the reviewer used the generalized estimation equations (GEE) approach for the analysis of repeated measures up to week 52 and week 104 in the analysis the ACR50 response data. The model included treatment group, visit, and treatment by visit interaction. The results are presented in Table 5.

Table 5. Reviewer's Analyses for ACR50

ACR50 Responses	MTX (1)	Adalimumab (2)	Adalimumab+MTX (3)	p-values (2) vs. (3)	(1) vs. (3)
Week 52					
Partial Imputation Responses/n (%)	118/210 (56.2)	113/225 (50.2)	165/220 (75.0)	<0.0001	<0.0001
GEE method Exp(LogOR)	1.0	1.4973	1.7622	0.1012	<0.0001
Week 104					
Partial Imputation Responses/n (%)	112/195 (57.4)	103/208 (49.5)	158/203 (77.8)	<0.0001	<0.0001
GEE method Exp(LogOR)	1.0	1.3949	1.5224	0.2522	<0.0001

The ACR 50 responses of Adalimumab+MTX were 1.8 and 1.5 times higher than that of MTX in odds ratio up to week 52 and week 104, respectively. There was no statistical difference between Adalimumab+MTX and Adalimumab.

For the change from baseline in TSS score, the Mann-Whitney test was used after partial imputing TSS scores.

Table 6. Reviewer's analyses for the change from baseline in TSS score at week 52

	MTX (1)	Adalimumab (2)	Adalimumab+MTX (3)	p-values (2) vs. (3)	(1) vs. (3)
TSS Score					
Week 52					
Partial Imputation, n	220	235	230		
Mean (SD)	27.6(24.4)	23.1(19.9)	19.6 (20.9)		
Median	22	19.5	14	<0.001	<0.001
Change from baseline					
Mean (SD)	5.0 (9.0)	3.2 (8.5)	0.97 (3.1)	<0.001	<0.001
Median	3.0	1.0	0.0		
Week 104					
Partial Imputation, n	195	208	203		
Mean (SD)	29.7(25.6)	25.2(20.7)	19.3 (20.8)		
Median	26.5	24	14.5	<0.001	<0.001
Change from baseline					
Mean (SD)	6.2 (11.1)	4.7 (9.2)	1.1 (4.0)	<0.001	<0.001
Median	3.5	2.0	0.0		

The Adalimumab +MTX group shows significantly less change from baseline TSS scores as compared to MTX group for both weeks 52 and 104.

The results of partial imputation methods for ACR50 and the change from baseline in modified TSS score were robust. The results of Adalimumab +MTX compared to MTX using the GEE method of ACR50 response at week 52 as well as week 104 were consistent to that of the sponsor, but not for the comparison between Adalimumab+MTX and Adalimumab (see Table 22).

This suggests that MTX-naïve subjects with recently diagnosed RA shows the most benefit for improving signs and symptoms and for inhibiting joint destruction with treatment of adalimumab + MTX combination therapy.

1.3.3. Statistical Issue

A potential issue could be the probability of dependent drop-out differs between the treated groups and the placebo group and this may lead to biased comparison of the effect if the missing data are ignored. More patients in the MTX group than in the adalimumab group and adalimumab +MTX group dropped out of the study due to lack of efficacy. This reviewer used the partial carrying forward imputation approach (Lynn Wei and Weichung J. Shiu, 2001) to avoid underestimated treatment effect by using LOCF or all available data approaches. The results were robust.

The reviewer used GEE analysis of the efficacy endpoint of the proportion of ACR50 responses as a supportive analysis. This supportive analysis also confirms the results of primary analysis.

Overall, this study supports the effectiveness of adalimumab 40 mg eow + MTX ≤ 20 mg/week combination treatment over MTX monotherapy treatment in the reduction in signs and symptoms and in inhibition of the progression of structural damage in subjects with recent-onset RA not previously treated with MTX.

2. INTRODUCTION

2.1 Overview

RA is a chronic, systemic, inflammatory and destructive autoimmune disease with clinical manifestations that primarily involve the synovial joints. RA affects approximately 1% of the population worldwide and commonly leads to severe, chronic functional disability, and consequently, to a reduced quality of life.

2.1.1 History of Drug Development

Adalimumab (HUMIRA®) is the first fully human anti-TNF monoclonal antibody engineered by gene technology. Adalimumab was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1: κ constant regions.

The many studies have demonstrated the potential benefit of early treatment with anti-TNF inhibitors alone or in combination with methotrexate (MTX) for recently diagnosed RA subjects. The Early Rheumatoid Arthritis (ERA) trial demonstrated that early intervention with anti-TNF monotherapy in subjects with RA for less than three years resulted in inhibition of disease progression that was as effective as MTX. Results from the ASPIRE study with infliximab and MTX in RA subjects with disease duration less than 3 years suggest that combining anti-TNF therapy with MTX provides significantly greater clinical benefit than MTX alone when administered earlier rather than later in the course of RA. Thus, early (average disease duration in these subjects was < 1 year) and aggressive treatment (with combination therapy) provides a unique opportunity to halt disease progression and offers the potential of disease remission.

Adalimumab is currently approved in over 50 countries worldwide to treat RA in adult subjects with moderately to severely active RA who have failed other disease-modifying anti-rheumatic drugs (DMARDs) using alone or in combination with MTX or other DMARDs.

The sponsor, Abbott Laboratories, conducted a multicenter, randomized, double-blind, active comparator-controlled, Phase III Study DE013 (PREMIER) to demonstrate the safety and efficacy of adalimumab + MTX combination therapy in the treatment of moderately to severely active RA in adult subjects who were recently diagnosed (< 3

years) and who had not been previously treated with MTX as one pivotal study. These data are submitted to support the indication extension for adalimumab to also treat recently diagnosed subjects with moderately to severely active RA who have not been previously treated with MTX.

2.1.2 Objectives in Treatment of RA

The objective of this trial was to examine the efficacy and safety of adalimumab in combination with methotrexate (MTX) vs. MTX monotherapy in the treatment of early rheumatoid arthritis.

The first primary objective was to assess the efficacy of adalimumab + MTX combination therapy *vs.* MTX monotherapy in reducing the signs and symptoms in subjects with early RA. The two co-primary endpoints are: the proportion of subjects who achieved ACR50 response at 52 weeks and the change from Baseline in modified Total Sharp Score (TSS) after 52 weeks. Safety was evaluated across the three treatment arms of the study: adalimumab + MTX combination therapy, MTX monotherapy, and adalimumab monotherapy.

Subjects of 799 were randomized in a 1:1:1 ratio to receive a combination of adalimumab 40 mg eow + MTX (≤ 20 mg/week), adalimumab 40 mg eow monotherapy, or MTX monotherapy (≤ 20 mg/week), and were treated for two years. This study was conducted approximately 100-120 centers.

This statistical review focuses mainly on the clinical study of Study DE013.

2.2 Data Sources

The sponsor provided electronic datasets for the Phase III study of DE013 (PREMIER). The datasets utilized for the review are as follows;
\\CBS5042329\M\EDR Submissions\2004BLA\DCC60000436\BLA125057\Compound\ABT-Humira\Humira sBLA-DE013\roadmap.pdf

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

3.1.1.1 Study Design

This study design was a multicenter, randomized, double-blind, active comparator-controlled, parallel-group, Phase III study of adalimumab in MTX-naïve subjects with early RA (defined as RA meeting American College of Rheumatology criteria and disease duration of less than 3 years).

Subjects were randomized 1:1:1 ratio to one of three treatment groups:

Group1: weekly MTX (≤20 mg/week)
Group2: adalimumab 40 mg eow,
Group3: adalimumab 40 mg eow together with weekly MTX (≤20 mg/week)
adalimumab administration was sc while MTX was given orally.

All subjects received oral concomitant folic acid 5 to 50 mg/week. The primary and major secondary analyses compared adalimumab + MTX combination therapy with MTX monotherapy. Adalimumab + MTX combination therapy and adalimumab monotherapy were compared for other secondary endpoints only.

The study included a Screening period, a 4-week washout period for subjects taking previous disease modifying anti-rheumatic drugs (DMARDs), a blinded two-year treatment period, and a 3-year open-label extension period for those who completed the blinded period. As follow-up, all subjects, irrespective of study completion or discontinuation, were to be examined at one month following their last injection of adalimumab. The total study duration was approximately 36 months with individual subject participation of up to 108 weeks for the active phase and, in total, 121 weeks including the post-study follow-up period.

3.1.1.2 Efficacy Endpoints

The primary efficacy endpoints are following:

- The proportion of subjects with ACR50 response at 52 weeks for adalimumab + MTX combination therapy was compared with that of MTX monotherapy for the reduction of signs and symptoms in subjects with early RA.

- Change from Baseline in modified TSS at Week 52 for adalimumab + MTX combination therapy compared with MTX monotherapy in the inhibition of radiographic progression.

Major secondary efficacy endpoints comparing adalimumab + MTX combination therapy and MTX monotherapy, ranked in the following order, included:

1. Improvement of physical function as measured by the change from Baseline in the Disability Index of the HAQ at Week 52
2. Proportion of subjects who achieved an ACR50 response at Week 104
3. Change from Baseline in modified TSS at Week 104
4. Proportion of subjects who achieved clinical remission, defined as DAS28 <2.6 at Week 52
5. Change from Baseline in the physical component of the SF-36® at Week 52
6. Proportion of subjects achieving a major clinical response defined as an ACR70 response for any six continuous months
7. Change from Baseline in the mental component of the SF-36® at Week 52.

3.1.1.3 Statistical Methods

The statistical tests were to be performed in a hierarchical manner to protect type I error. First, the primary analysis on signs and symptoms as described in the statistical analysis plan was to be performed. If there was a statistically significant difference in favor of adalimumab + MTX combination treatment compared with MTX monotherapy, the second primary analysis of inhibition of radiographic progression was to be performed. Otherwise, the analysis of inhibition of radiographic progression was to be considered as a secondary analysis.

The primary endpoint of ACR50 at week 52 was analyzed using Pearson's Chi-square test with the intent-to-treat principle, all subjects who were randomized and received at least one dose of double-blinded study medication.

Two sensitivity analyses were performed to assess the robustness of the statistical analysis on ACR50 response at Week 52. Data were analyzed as observed (i.e., completer population) and using the LOCF approach.

The Mann Whitney test was used for the analysis of the second primary efficacy endpoint for TSS. Subjects in full analysis set were included in this conditional primary analysis. Missing values for TSS were imported by a pre-defined linear progression method.

Sensitivity analyses were also performed to assess the robustness of the co-primary statistical analysis of change from Baseline in modified TSS at Week 52. These sensitivity analyses included using LOCF methods, observed values, an ANOVA model, and 75th percentile.

All secondary endpoints were to be analyzed in an analogous manner to the primary endpoint. For categorical endpoints (*e.g.,* ACR20, ACR50 or ACR70), Chi-square tests for comparison of proportions were used. For continuous endpoints (*e.g.,* DAS), ANOVA or ANCOVA models were to be applied.

As an alternative to the sponsor's primary analysis of ACR50 response at Week 52, the reviewer used the generalized estimation equations approach for the analysis of repeated measures up to week 52 and week 104 to analysis the ACR50 response data.

The reviewer used the partial imputation methods (Lynn Wei and Weichung J. Shiu, 2001) by partially imputing the missing data with LOCF to create similar drop-out rates among the thee treatment groups, so that the sample distribution of the follow-up time in the three arms become equal and dependence between response variable and the drop-out process in the three groups are equal. This partial imputation approach is recommended to be applied to estimation or test of the treatment difference because this approach provides unbiased estimation of the treatment effects and empirical coverage of the 95% confidence intervals very close to the normal level.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Among 1279 subjects who underwent screening procedures, a total of 799 subjects were randomized and received at least one dose of double-blinded study medication. A total of 539 subjects were completed 2 years: 169 (65.8%) who received MTX monotherapy, 167 (60.9%) who received adalimumab monotherapy, and 203 (75.7%) who received adalimumab + MTX combination therapy.

A summary of the number of subjects who entered Study DE013, their final status, and primary reason for study discontinuation at 52 weeks and 104 weeks are presented in Table 7.

Table 7. Disposition of Subjects at Weeks 52 and 104 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Week 52			
Number of subjects completing 1 year, n (%)	196 (76.3)	194 (70.8)	220 (82.1)
Subjects who prematurely terminated	61 (23.7)	80 (29.2)	48 (17.9)
Primary reason, n (%)			
Planned selection criteria, n (%)	0	1 (0.4)	0
Adverse Event, n (%)	14 (5.4)	19 (6.9)	22 (8.2)
Lost to follow-up, n (%)	0	0	0
Recovery, n (%)	0	0	0
Protocol violation, n (%)	4 (1.6)	2 (0.7)	2 (0.7)
Death, n (%)	1 (0.4)	1 (0.4)	0
Withdrew consent, n (%)	8 (3.1)	13 (4.7)	7 (2.6)
Lack of efficacy and/or progression of study disease, n (%)	32 (12.5)	43 (15.7)	12 (4.5)
Administrative reasons, n (%)	2 (0.8)	1 (0.4)	5 (1.9)
Week 104			
Number of Subjects Completing 2 years, n (%)	169 (65.8)	167 (60.9)	203 (75.7)
Subjects who prematurely terminated	88 (34.2)	107 (39.1)	65 (24.3)
Primary reason, n (%)			
Planned selection criteria, n (%)	0	1 (0.4)	0
Adverse Event, n (%)	19 (7.4)	26 (9.5)	32 (11.9)
Lost to follow-up, n (%)	0	0	1 (0.4)
Recovery, n (%)	1 (0.4)	0	0
Protocol violation, n (%)	6 (2.3)	6 (2.2)	4 (1.5)
Death, n (%)	1 (0.4)	3 (1.1)	0
Withdrew consent, n (%)	13 (5.1)	17 (6.2)	7 (2.6)
Lack of efficacy and/or progression of study disease, n (%)	46 (17.9)	52 (19.0)	13 (4.9)
Administrative reasons, n (%)	2 (0.8)	2 (0.7)	8 (3.0)

Overall, a total of 260 subjects prematurely terminated the study: 88 (34.2%) who received MTX monotherapy, 107 (39.1%) who received adalimumab monotherapy, and 65 (24.3%) who received adalimumab + MTX combination therapy. Of the subjects who completed the 2-year double-blind period of the study, only 13 (4.9%) subjects in the adalimumab + MTX combination group withdrew due to a primary reason of lack of efficacy compared to 52 (19.0%) subjects in the adalimumab monotherapy group and 46 (17.9%) subjects in the MTX monotherapy group. Of these, a total of 32 (11.9%) subjects

in the adalimumab + MTX combination therapy group, 26 (9.5%) subjects in the adalimumab monotherapy group, and 19 (7.4%) subjects in the MTX monotherapy group withdrew due to AEs as a primary reason. Subject disposition at Week 52 was comparable to that observed at Week 104.

The reviewer summarizes for the dropout rates by each visit week in Figure 1.

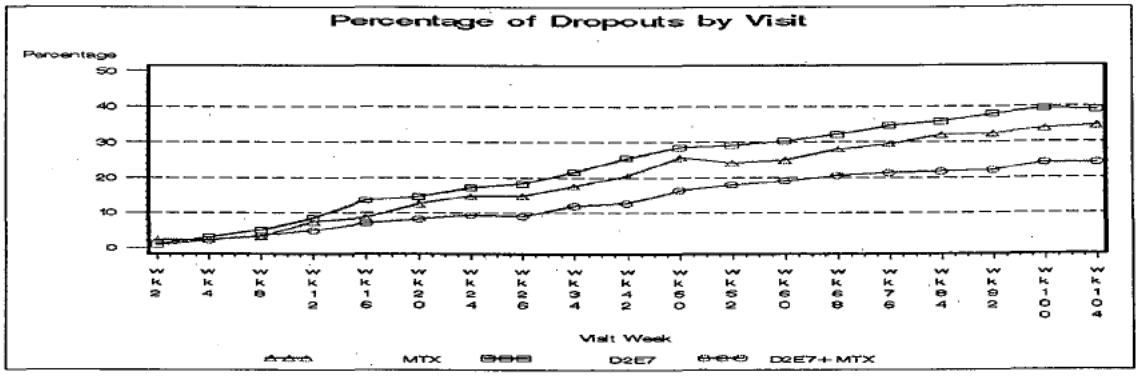

Figure 1 Plot of percentage dropouts by visit

The dropout rates increases rapidly after week 12 with the highest increasing rate of adalimumab monotherapy group and higher increasing rate of MTX group as compared to adalimumab + MTX combination group over week 104 visits.

The following demographic characteristics are summarized at baseline for all subjects in the full analysis set and are presented in Table 8.

Table 8. Demographic Characteristics (Full Analysis Set)

Demographic Characteristic	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[a]
Age (years)				
Mean ± SD	52.0 ± 13.1	52.1 ± 13.5	51.9 ± 14.0	0.992
Median	53	53	53	
Range	18 - 82	18 - 80	19 - 81	
Age group, n (%)				0.858
<40	43 (16.7)	54 (19.7)	52 (19.4)	
40 - 64	169 (65.8)	173 (63.1)	161 (60.1)	
65 - 74	33 (12.8)	36 (13.1)	42 (15.7)	
≥75	12 (4.7)	11 (4.0)	13 (4.9)	
Sex, n (%)				0.349
Female	190 (73.9)	212 (77.4)	193 (72.0)	
Male	67 (26.1)	62 (22.6)	75 (28.0)	
Race, n (%)				0.604
White	242 (94.2)	256 (93.4)	250 (93.3)	
Black	7 (2.7)	8 (2.9)	8 (3.0)	
Asian	1 (0.4)	3 (1.1)	6 (2.2)	
Other	7 (2.7)	7 (2.6)	4 (1.5)	
Body weight (kg)				
Mean ± SD	75.5 ± 17.9	74.4 ± 17.8	76.8 ± 17.9	0.281
Median	72.1	71.0	74.2	
Range	43.5 - 155.9	39.1 - 186.0	44.0 - 159.0	

a. The p-value was calculated from an analysis of variance comparing the three treatment groups.

The majority of the subjects were women (74.5%). Of the 799 randomized subjects, 748 (93.6%) were Caucasian and the remaining subjects were Black (23, 2.9%), Asian (10, 1.3%), or "Other" (18, 2.3%) race group. The median age of the subjects in this study was 53 years (range: 18 to 82 years). Three groups showed balanced demographic configuration.

Baseline disease characteristics were reflective of an early RA population and were generally comparable among the three treatment groups. A summary of Baseline disease characteristics is presented for each treatment group in Table 9.

Table 9. Baseline Disease Characteristics (Full Analysis Set)

Disease Characteristic	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[a]
Duration of RA (years)				
Mean ± SD	0.8 ± 0.9	0.7 ± 0.8	0.7 ± 0.8	0.204
Median (range)	0.4 (0.0 - 3.2)	0.4 (0.0 - 3.8)	0.4 (0.0 - 3.1)	
Duration of RA, n(%)				0.759
0.0 - 0.5, years	138 (53.7)	160 (58.4)	156 (58.2)	
0.5 - 1.0, years	37 (14.4)	40 (14.6)	42 (15.7)	
1.0 - 2.0, years	42 (16.3)	43 (15.7)	41 (15.3)	
2.0 - 3.0, years	36 (14.0)	26 (9.5)	27 (10.1)	
>/=3.0, years	4 (1.6)	5 (1.8)	2 (0.7)	
Baseline corticosteroid use, n (%)				0.995
Yes	91 (35.4)	100 (36.5)	96 (35.8)	
No	166 (64.6)	174 (63.5)	172 (64.2)	
Baseline RF, n (%)				0.900
Negative	41 (16.0)	45 (16.4)	40 (14.9)	
Positive	215 (83.7)	227 (82.8)	228 (85.1)	
Missing	1 (0.4)	2 (0.7)	0	

RA: rheumatoid arthritis; RF: rheumatoid factor

a. The p-value was calculated from an analysis of variance or chi-square test comparing the three treatment groups.

Efficacy parameters at Baseline are summarized in Table 10.

Table 10. Efficacy Parameters at Baseline (Full Analysis Set)

Efficacy Parameter	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[a]
Tender Joint Count (68)				
N	257	274	268	
Mean ± SD	32.3 ± 14.3	31.8 ± 13.6	30.7 ± 14.2	0.392
Median	31.0	29.5	29.0	
Range	11.0 – 66.0	11.0 – 66.0	5.0 – 68.0	
Swollen Joint Count (66)				
N	257	274	268	
Mean ± SD	22.1 ± 11.7	21.8 ± 10.5	21.1 ± 11.2	0.595
Median	19.0	20.0	18.0	
Range	8.0 – 62.0	8.0 – 57.0	8.0 – 63.0	
C-reactive protein (mg/dL)				
N	257	274	268	
Mean ± SD	4.0 ± 4.0	4.1 ± 3.9	3.9 ± 4.2	0.781
Median	2.6	2.7	2.4	
Range	0.4 – 25.1	0.4 – 19.4	0.4 – 20.7	
Disability Index of HAQ				
N	256	272	266	
Mean ± SD	1.48 ± 0.67	1.63 ± 0.62	1.47 ±0.64	0.011
Median	1.50	1.63	1.50	
Range	0.00 – 3.00	0.00 – 3.00	0.00 – 2.88	
DAS28-4 (including general health)				
N	251	270	257	
Mean ± SD	6.335 ± 0.873	6.367 ± 0.921	6.304 ± 0.937	0.734
Median	6.278	6.397	6.286	
Range	4.001 – 8.419	3.854 – 8.444	3.847 – 8.578	
FACIT-F				
N	255	272	265	
Mean ± SD	28.98 ± 11.05	26.20 ± 11.32	28.43 ± 11.66	0.012
Median	30.00	25.00	29.00	
Range	1.00 – 52.00	1.00 – 49.00	0.00 – 52.00	
Patient's Assessment of Pain (100 mm VAS)				
N	256	273	265	
Mean ± SD	59.6 ± 24.3	64.6 ± 23.6	62.5 ± 21.3	0.041
Median	61.5	70.0	65.0	
Range	2.0 – 100.0	4.0 – 100.0	3.0 – 100.0	
Morning Stiffness, n (%)				0.947
Yes	252 (98.1)	267 (97.4)	263 (98.1)	
No	5 (1.9)	7 (2.6)	5 (1.9)	
Duration of morning stiffness (minutes)				
N	254	271	266	
Mean ± SD	142.9 ± 113.8	141.5 ± 104.2	133.8 ±107.1	0.582
Median	120.0	120.0	120.0	
Range	0.0 – 360.0	5.0 – 360.0	0.0 – 360.0	
Modified TSS				
N	251	271	267	
Mean ± SD	21.9 ± 22.2	18.8 ± 19.0	18.1 ± 20.1	0.086
Median	15.5	13.5	13.0	
Range	0.0 – 149.5	0.0 – 110.5	0.0 – 137.5	
Erosion Score				
N	251	271	267	
Mean ± SD	13.6 ± 13.6	11.3 ± 11.3	11.0 ± 12.3	0.030
Median	9.5	8.5	7.5	
Range	0.0 – 75.5	0.0 – 67.5	0.0 – 98.5	
Subjects with at least one erosion at Baseline				
N (%)	246 (95.7)	258 (94.2)	248 (92.5)	N/A
Joint Space Narrowing Score				
N	251	271	267	
Mean ± SD	8.2 ± 10.7	7.5 ± 9.4	7.1 ± 9.6	0.443
Median	4.5	4.5	4.5	
Range	0.0 – 84.0	0.0 – 74.0	0.0 – 68.5	

DAS: disease activity score; HAQ: Health Assessment Questionnaire; FACIT-F: functional assessment of chronic illness therapy - fatigue; HUI 2/3: Health Utilities Index Mark 2/Mark 3; PaGA: Patient's Global Assessment; PGA: Physician's Global Assessment;

TSS: Total Sharp Score; VAS: visual analogue scale
a. The p-value was from an analysis of variance or chi-square test comparing the three treatment groups.

Efficacy parameters at Baseline were reflective of an RA population with moderate to severe disease. Baseline efficacy parameters were generally comparable among treatment groups; however, there were statistically significant differences in the Disability Index of the HAQ, FACIT-F, HUI 3, Patient's Global Assessment of Disease Activity, Patient's Assessment of Pain, and erosion score.

3.1.3 Primary Efficacy Results

Sponsor's Analysis Results

A summary of ACR50 response for the Full Analysis Set at Week 52 is presented in Table 11.

Table 11. ACR50 Response at Week 52 (All Randomized Subjects in the Two Treatment Groups)

	MTX (N = 257) n (%)	Adalimumab + MTX (N = 268) n (%)	p-value[a]
Week 52	118 (45.9)	165 (61.6)	<0.001

Note: Subjects who did not meet the aforementioned ACR50 criteria, discontinued prior to Week 52, and without sufficient data at Baseline to calculate ACR50 at Week 52 were considered non-responders. Subjects who completed Week 52 but did not have assessments performed to be evaluated according to the aforementioned criteria were assigned an ACR score of missing, and therefore were considered non-responders.
a. P-value is from Pearson's chi-square test of adalimumab + MTX vs. MTX.

Following 52 weeks of treatment, 61.6% (165/268) of subjects who received adalimumab + MTX combination therapy statistically highly achieved an ACR50 response compared to 45.9% (118/257) of subjects who received MTX monotherapy (p<0.001).

Two sensitivity analyses results of ACR50 response at Week 52 are presented in Table 12.

Table 12. ACR50 Response at Week 52 (Sensitivity Analyses)

	MTX	Adalimumab + MTX	p-value[a]
Week 52			
Observed			
Number of Evaluable Subjects	195	220	
Week 52 Responders, n (%)	118 (60.5)	165 (75.0)	0.002
LOCF			
Number of Evaluable Subjects	257	268	
Week 52 Responders, n (%)	118 (45.9)	166 (61.9)	<0.001

a. P-value is from a comparison between adalimumab + MTX combination therapy and MTX monotherapy using Pearson's chi-square test when cell sizes are > 5; otherwise, a continuity adjusted chi-square test was used.

The sensitivity analyses showed that the results of ACR50 response at Week 52 were consistent with those of the primary analysis, demonstrating that adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy in improving signs and symptoms in subjects with recently diagnosed moderate to severe RA.

Because the primary endpoint for the reduction of signs and symptoms was met (*i.e.*, ACR50 response at Week 52), analysis of the second co-primary endpoint, the change from Baseline in modified TSS at Week 52 for the inhibition of radiographic progression, was performed. An increase in modified TSS is indicative of disease progression and/or joint worsening. A summary of the change from Baseline in modified TSS at Week 52 is presented in Table 13.

Table 13. Change in Modified Total Sharp Score from Baseline at Week 52 (All Randomized Subjects in the Two Treatment Groups)

	MTX (N = 257)				Adalimumab + MTX (N = 268)				
	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range	p-value[a]
Baseline	252	21.8 ± 22.2	15.5	0.0 – 149.5	268	18.1 ± 20.1	13.3	0.0 – 137.5	
Week 52	252	27.6 ± 24.6	21.5	0.0 – 170.0	268	19.4 ± 19.9	14.3	0.0 – 141.5	
Change at Week 52	257	5.7 ± 12.7	2.5	-58.0 – 78.5	268	1.3 ± 6.5	0.0	-68.0 – 29.5	<0.001

Note: An increase in modified TSS is indicative of disease progression and/or joint worsening. In contrast, no change in modified TSS represents a halting of disease progression and a decrease represents improvement.
Note: Primary analysis imputation is used for missing data.
a. P-value is from the Mann-Whitney U test of adalimumab + MTX vs. MTX.

Following 52 weeks of treatment, subjects treated with adalimumab + MTX combination therapy had a statistically low mean increase of **1.3** Sharp units compared to **5.7** Sharp units in subjects treated with MTX monotherapy ($p<0.001$).

Four sensitivity analyses were performed to assess the robustness of the statistical analysis on change from Baseline in Modified TSS at Week 52 (Table 14). Data were analyzed as observed (*i.e.*, completer population) and using the LOCF approach, an ANOVA model, and 75th percentile for subjects missing Baseline or Week 52 x-rays.

Table 14. Change from Baseline in Modified TSS score (Sensitivity Analysis)

	MTX (N = 257)				Adalimumab + MTX (N = 268)				
	N	Mean ± SD	Median	Range	N	Mean ± SD	Median	Range	p-value
Observed									
Baseline	204	22.2 ± 22.5	15.8	0.0 - 149.5	229	18.6 ± 20.6	13.0	0.0 - 137.5	
Week 52	204	27.4 ± 25.3	19.8	0.0 - 170.0	229	19.6 ± 21.0	14.0	0.0 - 141.5	
Change at Week 52	204	5.2 ± 9.4	2.0	-6.5 - 78.5	229	1.0 ± 3.2	0.0	-6.0 - 21.5	<0.001[a]
LOCF									
Baseline	220	21.6 ± 22.1	15.5	0.0 - 149.5	244	18.2 ± 20.2	12.8	0.0 - 137.5	
Week 52	204	27.4 ± 25.3	19.8	0.0 - 170.0	229	19.6 ± 21.0	14.0	0.0 - 141.5	
Change at Week 52	220	5.2 ± 9.3	2.0	-6.5 - 78.5	244	1.0 ± 3.3	0.0	-9.0 - 21.5	<0.001[a]
ANOVA[b]									
Baseline	204	22.2 ± 22.5	15.8	0.0 - 149.5	229	18.6 ± 20.6	13.0	0.0 - 137.5	
Week 52	204	27.4 ± 25.3	19.8	0.0 - 170.0	229	19.6 ± 21.0	14.0	0.0 - 141.5	
Change at Week 52	204	5.2 ± 9.4	2.0	-6.5 - 78.5	229	1.0 ± 3.2	0.0	-6.0 - 21.5	<0.001[c]
75th Percentile[d]									
Baseline	251	21.9 ± 22.2	15.5	0.0 - 149.5	267	18.1 ± 20.1	13.0	0.0 - 137.5	
Week 52	205	27.4 ± 25.3	20.0	0.0 - 170.0	230	19.6 ± 20.9	14.0	0.0 - 141.5	
Change at Week 52	257	4.8 ± 8.4	3.5	-6.5 - 78.5	268	1.3 ± 3.1	0.5	-6.0 - 21.5	<0.001[a]

Note: An increase in modified TSS is indicative of disease progression and/or joint worsening. In contrast, no change in modified TSS represents a halting of disease progression and a decrease represents improvement.

a. P-value is from the Mann-Whitney U test of adalimumab + MTX vs. MTX.: b. observed data: c. P-value is from ANOVA.: d. The missing change from Baseline values for TSS are imputed using the 75th percentile of the non-missing change from Baseline scores for the two treatment groups.

The sensitivity analyses showed that the results of the change from Baseline in modified TSS at Week 52 are consistent with those of the primary analysis, demonstrating that adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy in inhibition of radiographic progression in subjects with recently diagnosed moderate to severe RA.

3.1.4 Sponsor's Major Secondary Efficacy analyses results

Analysis of the major secondary endpoints was performed in a conditional manner, similar to the primary endpoint analyses, until a non-significant p-value was reported.

1. Change from Baseline in the Disability Index of HAQ at Week 52

A summary of the change from Baseline in the Disability Index of HAQ at Week 52 is presented in Table 15.

Table 15. Change in the Disability Index of the HAQ Score from Baseline to Week 52 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value[a]
N	191	213	
Baseline (mean)	1.5	1.5	
Week 52 (mean)	0.7	0.4	
Change at Week 52 (mean ± SD)	-0.8 ± 0.6	-1.1 ± 0.6	<0.001

Note: An improvement in the Disability Index of the HAQ was represented by a negative mean change from Baseline to Week 52.

a. P-value is from the pairwise comparison of adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.

Following 52 weeks of treatment, subjects who received adalimumab + MTX combination therapy demonstrated a statistically significantly greater improvement (*i.e.*, decrease) in the Disability Index of the HAQ (**-1.1** units) compared to subjects who received MTX monotherapy (**-0.8** units; $p<0.001$).

2. ACR50 Response at Week 104

A summary of the ACR50 response, including sensitivity analyses using observed values (*i.e.*, completer population) and LOCF approach, at Week 104 is summarized in Table 16.

Table 16. ACR50 Response at Week 104 – Imputed, Observed, LOCF (All Randomized Subjects)

ACR50 at Week 104	MTX (N = 257) n (%)	Adalimumab + MTX (N = 268) n (%)	p-value
Imputed[a]			
Week 104 responders, n (%)	110 (42.8)	158 (59.0)	<0.001[b]
Observed			
Number of Evaluable Subjects	168	203	
Week 104 Responders, n (%)	110 (65.5)	158 (77.8)	0.008[c]
LOCF			
Number of Evaluable Subjects	257	268	
Week 104 Responders, n (%)	116 (45.1)	168 (62.7)	<0.001[c]

a. Imputed analysis in which subjects with missing values were counted as non-responders.

b. P-value is from the chi-square test of adalimumab + MTX vs. MTX.

c. P-value is from the Pearson's chi-square test adalimumab + MTX vs. MTX when cell sizes are > 5; otherwise, a continuity adjusted chi-square test was used.

Following 104 weeks of treatment, 59.0% (158/268) of subjects who received adalimumab + MTX combination therapy achieved an ACR50 response compared to 42.8% (110/257) of subjects who received MTX monotherapy ($p<0.001$). Results of the sensitivity analyses showed the robustness of the statistical analysis of ACR50 at Week 104.

3. Change from Baseline in Modified Total Sharp Score at Week 104

A summary of the change from Baseline in modified TSS at Week 104 (missing values were imputed), including sensitivity analyses using observed values (*i.e.*, completer population) and LOCF approach, is presented in Table 17.

Table 17. Change in Modified Total Sharp Score from Baseline at Week 104 – Imputed, Observed, LOCF (All Randomized Subjects)

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value[a]
Imputed			
Baseline (mean)	21.8 ± 22.2	18.1 ± 20.1	
Week 104 (mean)	32.3 ± 30.0	20.0 ± 20.5	
Change at Week 104 (mean ± SD)	**10.4** ± 21.7	**1.9** ± 8.3	<0.001
Observed			
N	172	202	
Baseline (mean)	22.9 ± 22.9	18.2 ± 20.5	
Week 104 (mean)	29.3 ± 27.3	19.3 ± 20.9	
Change at Week 104 (mean ± SD)	6.4 ± 11.8	1.1 ± 4.0	<0.001
LOCF			
N	220	244	
Baseline (mean)	21.6 ± 22.1	18.2 ± 20.2	
Week 104 (mean)	29.3 ± 27.3	19.3 ± 20.9	
Change at Week 104 (mean ± SD)	7.0 ± 12.3	1.2 ± 4.1	<0.001

Note: An increase in modified TSS is indicative of disease progression and/or joint worsening. In contrast, no change in modified TSS represents a halting of disease progression and a decrease represents improvement.
a. P-value is from the Mann-Whitney U test.

Following 104 weeks of treatment, subjects treated with adalimumab + MTX combination therapy had a mean increase from Baseline of 1.9 Sharp units compared to 10.4 Sharp units in subjects treated with MTX monotherapy ($p<0.001$).

Sensitivity analysis using LOCF and analysis of observed data regarding the change from Baseline in modified TSS at Week 104 showed similar results.

4. Subjects in Clinical Remission as Defined by DAS28 <2.6 at Week 52

DAS28 has a scale from 0 to 10 indicating the current activity of RA. According to the European League Against Rheumatism (EULAR), DAS28 >5.1 indicates high disease activity and DAS28 <3.2 indicates low disease activity. Remission is indicated by DAS28 <2.6.
A summary of subjects in clinical remission defined as DAS28 <2.6 at Week 52 is presented in Table 18.

Table 18. Subjects in Clinical Remission as Defined by DAS28 <2.6 at Week 52 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab + MTX (N = 268)	
	n (%)	n (%)	p-value[a]
Subjects in remission at Week 52	53 (**20.6**)	115 (**42.9**)	<0.001

Note: Remission is defined as DAS28 < 2.6

a. P-value is from the pairwise comparison of adalimumab + MTX combination therapy and MTX monotherapy using the chi-square test.

Following 52 weeks of treatment, 42.9% (115/268) of subjects who received adalimumab + MTX combination therapy achieved clinical remission, as defined by DAS28 <2.6, compared to 20.6% (53/257) of subjects who received MTX monotherapy ($p<0.001$).

5. Change from Baseline in the Physical Component of SF-36® at Week 52

A summary of the mean change from Baseline in the physical component of the SF-36® at Week 52 is presented in Table 19.

Table 19. Change in the Physical Component of SF-36® from Baseline at Week 52 (All Randomized Subjects)

	MTX (N = 257)	Adalimumab + MTX (N = 268)	p-value[a]
N	181	198	
Baseline (mean)	29.9	28.8	
Week 52 (mean)	42.5	45.5	
Change at Week 52 (Mean ± SD)	**12.5** ± 9.6	**16.7** ± 10.2	<0.001

a. P-value is from the pairwise comparison of adalimumab + MTX combination therapy and MTX monotherapy using the Mann-Whitney U test.

Following 52 weeks of treatment, subjects who received adalimumab + MTX combination therapy demonstrated a statistically significantly greater improvement (increase) from Baseline in the physical component of the SF-36® (**16.7**) compared to subjects who received MTX monotherapy (**12.5**; $p<0.001$).

6. Major Clinical Response (ACR70) Over 104 Weeks of Treatment

A summary of major clinical response, defined as an ACR70 response for any six continuous months, over 104 weeks of treatment is presented in Table 20.

Table 20. Major Clinical Response Over 104 Weeks of Treatment (All Randomized Subjects)

	MTX (N = 257) n (%)	Adalimumab + MTX (N = 268) n (%)	p-value[a]
Subjects with major clinical response at Week 104	70 (27.2)	130 (**48.5**)	<0.001

Note: Major clinical response is defined as a continuous ACR70 response for 6 continuous months.
a. P-value is from the the chi-square test of adalimumab + MTX vs. MTX.

Following 104 weeks of treatment, **48.5%** (130/268) of subjects who received

adalimumab + MTX combination therapy achieved a major clinical response, defined as an ACR70 response for any six continuous months, compared to **27.2%** (70/257) of subjects who received MTX monotherapy ($p<0.001$).

7. Change from Baseline in the Mental Component of the SF-36® at Week 52

A summary of the mean change from Baseline in the mental component of the SF-36® at Week 52 is presented in Table 21.

Table 21. Change in the Mental Component of SF-36® from Baseline at Week 52 (All Randomized Subjects)

	MTX (N =257)	Adalimumab + MTX (N = 268)	p-value[a]
N	181	198	
Baseline (mean)	45.3	44.8	
Week 52 (mean)	51.8	52.0	
Change at Week 52 (Mean ± SD)	6.5 ± 11.0	7.2 ± 13.1	0.5402

a. P-value is from the Mann-Whitney U test of adalimumab + MTX vs. MTX.

Following 52 weeks of treatment, similar improvements in the mental component of the SF-36® was seen in subjects treated with adalimumab + MTX combination therapy (7.2) compared to subjects treated with MTX monotherapy (6.5).

All of the major secondary endpoints demonstrated the statistical superiority of adalimumab + MTX combination therapy compared to MTX monotherapy except the mental component of the SF-36® at Week 52 (Table 15 through Table 21).

Adalimumab + MTX combination therapy was found to be clinically and statistically superior to MTX monotherapy in improvement of physical function, improvement of signs and symptoms, inhibition of radiographic progression, achievement of clinical remission as defined by DAS28 <2.6, improvement in the physical aspect of QoL, and achievement of a major clinical response defined as an ACR70 response for six continuous months. For the mental component of the SF-36®, adalimumab + MTX combination therapy was no statistically significantly difference compared to MTX monotherapy.

3.1.5 Reviewer's Additional Analyses Results

The reviewer used the generalized estimation equations approach with repeated measures of ACR50 responses up to week 52 and week 104 visits for a supportive analysis for the primary efficacy analysis. The model included treatment group, visit and treatment by visit interaction. The results are summarized in Table 22.

Table 22. The results of ACR50 response up to weeks 52 and 104 in the GEE analyses

	Estimated Log Odds				
	(1) MTX	(2) Adalimumab	(3) Adalimumab +MTX	p-value (3) vs. (2)	(3) vs. (1)
Week 52					
Exp(LogOR)	1.0	1.4973	1.7622	0.1012	<0.0001
Week 104					
Exp(LogOR)	1.0	1.3949	1.5224	0.2522	<0.0001

The ACR50 responses up to week 52 and week 104 of adalimumab +MTX group are higher than that of MTX and adalimumab monotherapy groups (1.76 times and 1.50 times in odds ratio at week 52 and 1.52 times and 1.40 times in odds ratios at week 104, respectively) and the results were consistent to the sponsor's results. There was no difference between adalimumab and adalimumab+MTX in the ACR50 responses up to week 52 and week 104 in the GEE analyses.

The reviewer summarizes the percentage of ACR50 by visit week in Figure 2.

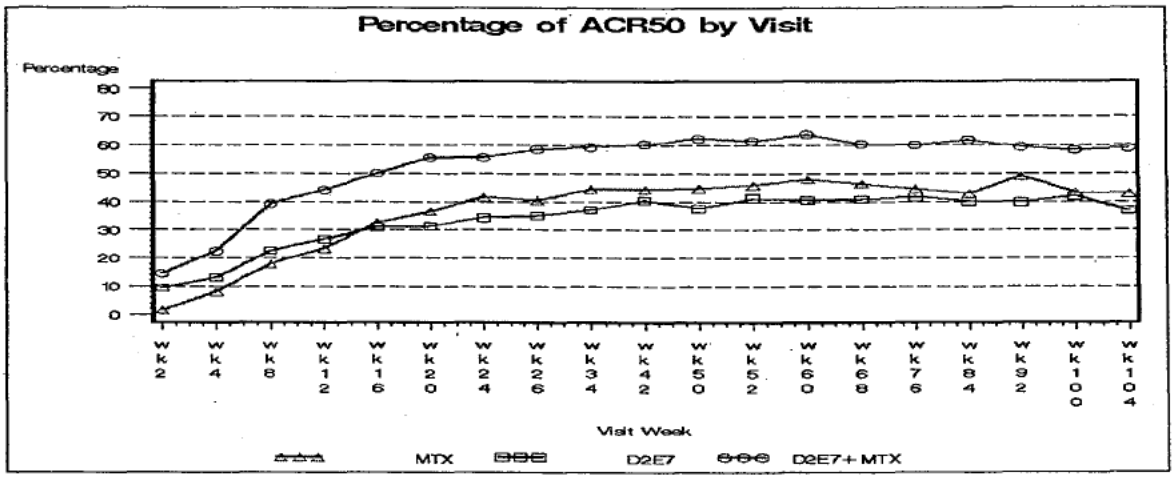

Figure 2. The percentage of ACR50 by visit week

ACR50 response rates were statistically significantly higher in adalimumab + MTX group than that of MTX group all visit weeks, but there was no statistical difference in adalimumab monotherapy group compared to MTX monotherapy group except from week 2 to week 12.

The reviewer's sensitivity analyses for ACR50 and change from baseline in modified TSS score using partial imputation methods were summarized in Table 23 and Table 24, respectively.

Table 23. Reviewer's Sensitivity Analysis of ACR50 using the Partial Imputation Method

	(1) MTX (N=257)	(2) Adalimumab (N=274)	(3) Adalimumab +MTX (N=268)	p-values (3) vs. (2)	p-values (3) vs. (1)
At week 52					
Number of subjects, n, (%)	210 (81.7)	225 (82.1)	220 (82.0)		
Number of responders, n, (%)	118 (56.2)	113 (50.2)	165 (75.0)	<0.0001	<0.0001
At week 104					
Number of subjects, n, (%)	195 (75.9)	208 (75.9)	203(75.7)		
Number of responders, n, (%)	112 (57.4)	103 (49.5)	158 (77.8)	<0.0001	<0.0001

The results of ACR50 using the partial imputation method were robust.

Table 24. Reviewer's Sensitivity Analysis of Change from Baseline in Modified TSS score using the Partial Imputation Method

	MTX (N=257)				Adalimumab+MTX(N=268)				
	N	Mean(SD)	Median	Range	N	Mean(SD)	Median	Range	p-value
At week 52									
Week 52	220	27.6 (24.4)	22.0	(21.8, 170)	230	19.6 (20.9)	14	(18.5, 141.5)	<0.001
Change	220	5.0 (9.0)	3.0	(6.5, 85)	229	0.97 (3.21)	0.0	(1.5, 27.5)	<0.001
At Week 104									
Week 104	195	29.7 (25.6)	26.5	(26, 165)	203	19.3 (20.8)	14.5	(18, 141)	<0.001
Change	195	6.2 (11.1)	3.5	(7.5, 102)	202	1.1 (4.0)	0.0	(2, 39)	<0.001

	Adalimumab (N=274)				Adalimumab+MTX(N=268)				
	N	Mean(SD)	Median	Range	N	Mean(SD)	Median	Range	p-value
At week 52									
Week 52	235	13.1 (19.9)	19.5	(22.5, 109.5)	230	19.6 (20.9)	14	(18.5, 141.5)	<0.001
Change	235	3.2 (8.5)	1.0	(3.5, 110)	229	0.97 (3.21)	0.0	(1.5, 27.5)	<0.001
At Week 104									
Week 104	208	25.2 (20.7)	24.0	(22.5, 139)	203	19.3 (20.8)	14.5	(18, 141)	<0.001
Change	208	4.7 (9.2)	4.5	(4.5, 82)	202	1.1 (4.0)	0.0	(2, 39)	<0.001

The results of change from baseline in modified TSS score using the partial imputation method were also robust.

The analysis of both primary endpoints, the proportion of subjects who achieved an

ACR50 response and the change from Baseline in modified TSS following 52 weeks of treatment, demonstrated that adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy in improving signs and symptoms and inhibiting progression of radiographic progression in subjects with recently diagnosed moderate to severe RA.

3.2 Evaluation of Safety

Safety was assessed by AEs, physical examination, vital signs and laboratory data. The safety analysis set included all subjects who received at least one dose of study drug (MTX monotherapy = 257, adalimumab monotherapy = 274, adalimumab + MTX combination therapy = 268).

Table 25. Overview of Subjects with Treatment-Emergent Adverse Events (Safety Analysis Set)

Number (%) of Subjects with Treatment-Emergent Adverse Events[a,b]	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)	p-value[c]
Any AE	245 (95.3)	262 (95.6)	262 (97.8)	0.269
Any SAE	43 (16.7)	63 (23.0)	55 (20.5)	0.192
Any severe AE	49 (19.1)	67 (24.5)	68 (25.4)	0.176
Any at least possibly drug-related AE	171 (66.5)	179 (65.3)	187 (69.8)	0.524
Any AE leading to death	1 (0.4)	4 (1.5)	1 (0.4)	0.381
Any AE leading to discontinuation	29 (11.3)	38 (13.9)	34 (12.7)	0.670
Any AE leading to dose interruption	82 (31.9)	85 (31.0)	103 (38.4)	0.143
Any infectious AE	175 (68.1)	185 (67.5)	207 (77.2)	0.020[d]
Any serious infectious AE	7 (2.7)	3 (1.1)	13 (4.9)	0.033[e]
Any AE of immunologic reaction	1 (0.4)	7 (2.6)	3 (1.1)	0.096
Any AE of serious immunologic reaction	0	1 (0.4)	1 (0.4)	1.000
Any AE of malignancies (excluding non-melanoma skin cancers)	4 (1.6)	4 (1.5)	2 (0.8)	0.727
All AEs of malignancies	5 (2.0)	4 (1.5)	6 (2.2)	0.807

AE: adverse event; SAE: serious adverse event

a. See Section 12.2 for definition of treatment-emergent AE.

b. Subjects may be counted in more than one AE parameter.

c. P-values are from chi-square test (Fisher's Exact Test if >=20% of the cells have expected cell count <5).

d. P-values: MTX *vs.* adalimumab + MTX, p=0.024; adalimumab *vs.* adalimumab + MTX, p=0.013.

e. P-values: MTX *vs.* adalimumab + MTX, p=0.256; adalimumab *vs.* adalimumab + MTX, p=0.011.

Subjects in adalimumab +MTX group reported higher any infectious AE as compared to the subjects in adalimumab and MTX monotherapy groups (p=0.013 and p=0.024, respectively. Also, significantly higher any serious infectious AE were observed in the adalimumab+MTX treated subjects (p=0.011) as compared to adalimumab monotherapy treated subjects.

A summary of treatment-emergent AEs, irrespective of relationship to study drug, that occurred in more than 5% of subjects in any treatment group is presented in Table 26. Within each MedDRA SOC in Table 26, AEs are sorted by descending frequency in the adalimumab + MTX treatment group.

Table 26. Number (%) of Subjects with the Most Frequent (>5% of Subjects in Any Treatment Group) Treatment-Emergent Adverse Events, Irrespective of Relationship to Study Drug (Safety Analysis Set)

Adverse Event[a,b] System Organ Class Preferred Term	MTX (N = 257)	Adalimumab (N = 274)	Adalimumab + MTX (N = 268)
Any Adverse Event	245 (95.3)	262 (95.6)	262 (97.8)
Blood and Lymphatic System Disorders			
Lymphadenopathy	13 (5.1)	15 (5.5)	1 (0.4)
Gastrointestinal Disorders			
Nausea	52 (20.2)	46 (16.8)	45 (16.8)
Dyspepsia	26 (10.1)	22 (8.0)	30 (11.2)
Diarrhea NOS	35 (13.6)	26 (9.5)	26 (9.7)
Abdominal Pain Upper	22 (8.6)	19 (6.9)	24 (9.0)
Abdominal Pain NOS	10 (3.9)	12 (4.4)	17 (6.3)
Mouth Ulceration	18 (7.0)	10 (3.6)	13 (4.9)
Constipation	15 (5.8)	3 (1.1)	8 (3.0)
General Disorders and Administration Site Conditions			
Fatigue	20 (7.8)	24 (8.8)	23 (8.6)
Influenza Like Illness	12 (4.7)	9 (3.3)	14 (5.2)
Infections and Infestations			
Nasopharyngitis	65 (25.3)	61 (22.3)	82 (30.6)
Upper Respiratory Tract Infection NOS	46 (17.9)	23 (8.4)	50 (18.7)
Pharyngitis NOS	26 (10.1)	28 (10.2)	29 (10.8)
Sinusitis NOS	18 (7.0)	23 (8.4)	29 (10.8)
Herpes Simplex	9 (3.5)	8 (2.9)	21 (7.8)
Urinary Tract Infection NOS	23 (8.9)	31 (11.3)	22 (8.2)
Bronchitis NOS	25 (9.7)	14 (5.1)	17 (6.3)
Influenza	14 (5.4)	17 (6.2)	10 (3.7)
Investigations			
Alanine Aminotransferase Increased	10 (3.9)	7 (2.6)	21 (7.8)
Liver Function Tests NOS Abnormal	12 (4.7)	6 (2.2)	21 (7.8)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	26 (10.1)	37 (13.5)	27 (10.1)
Back Pain	28 (10.9)	31 (11.3)	23 (8.6)
Arthritis NOS Aggravated	28 (10.9)	41 (15.0)	21 (7.8)
Pain in Limb	9 (3.5)	10 (3.6)	18 (6.7)
Rheumatoid Arthritis Aggravated	16 (6.2)	21 (7.7)	12 (4.5)
Joint Swelling	12 (4.7)	15 (5.5)	5 (1.9)
Nervous System Disorders			
Headache NOS	41 (16.0)	56 (20.4)	53 (19.8)
Dizziness (excluding Vertigo)	15 (5.8)	23 (8.4)	20 (7.5)
Paraesthesia	7 (2.7)	14 (5.1)	8 (3.0)
Psychiatric Disorders			
Depression NOS	15 (5.8)	10 (3.6)	17 (6.3)
Insomnia	6 (2.3)	14 (5.1)	9 (3.4)
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	22 (8.6)	30 (10.9)	24 (9.0)
Dyspnoea NOS	7 (2.7)	17 (6.2)	10 (3.7)
Skin and Subcutaneous Tissue Disorders			
Contusion	7 (2.7)	6 (2.2)	19 (7.1)
Alopecia	13 (5.1)	11 (4.0)	18 (6.7)
Rash NOS	17 (6.6)	19 (6.9)	8 (3.0)
Vascular Disorders			
Hypertension NOS	20 (7.8)	19 (6.9)	17 (6.3)

a. See Section 12.2 for definition of treatment-emergent AE.
b. More than one AE category per subject possible.

The profile of most commonly reported treatment-emergent AEs was similar across treatment groups. Nasopharyngitis was the most frequent event in each group. This AE,

along with headache NOS, nausea, diarrhea NOS, arthralgia, and pharyngitis, were all among the ten most commonly reported AEs in each group.

AEs reported by > 5% of subjects that occurred notably more frequently (5% difference in percentage between groups) in subjects treated with adalimumab + MTX combination therapy than in those treated with MTX monotherapy included nasopharyngitis, while the only AEs that occurred notably less frequently in subjects treated with adalimumab + MTX combination therapy than in subjects treated with MTX monotherapy was lymphadenopathy. The most common AEs in the adalimumab + MTX group were nasopharyngitis, headache NOS, upper respiratory tract infection NOS, nausea, dyspepsia, pharyngitis NOS, sinusitis NOS, and arthralgia. There are common events and typically do not represent any clinically significant safety issues for the subject.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The subgroup analyses based on demographic characteristics for the primary efficacy endpoint are summarized in Tables 27 and 28.

Table 27. ACR50 Response at Week 52 by Subgroups (All Randomized Subjects)

	MTX (N = 257)		Adalimumab + MTX (N = 268)		
	N	n (%)	N	n (%)	p-value[a]
Sex					
Male	67	30 (44.8)	75	52 (69.3)	0.003
Female	190	88 (46.3)	193	113 (58.5)	0.017
Age (years)					
<40	43	19 (44.2)	52	37 (71.2)	0.008
40-64	169	80 (47.3)	161	98 (60.9)	0.014
65-74	33	15 (45.5)	42	22 (52.4)	0.551
>=75	12	4 (33.3)	13	8 (61.5)	0.313
Race					
White	242	110 (45.5)	250	159 (63.6)	<0.001
Black	7	3 (42.9)	8	2 (25.0)	0.855
Asian	1	1 (100.0)	6	3 (50.0)	1.000
Other	7	4 (57.1)	4	1 (25.0)	0.689
Weight quartiles (kg)					
0 - <63	68	30 (44.1)	55	39 (70.9)	0.003
>=63 - <73	65	35 (53.8)	69	42 (60.9)	0.411
>=73 - <85.5	60	25 (41.7)	74	50 (67.6)	0.003
>=85.5 - <159	64	28 (43.8)	70	34 (48.6)	0.576
Height quartiles (cm)					
0 - <160	56	23 (41.1)	67	38 (56.7)	0.084
>=160 - <165	62	32 (51.6)	51	33 (64.7)	0.161
>=165 - <173	68	31 (45.6)	81	41 (50.6)	0.541
>=173 - <200	71	32 (45.1)	69	53 (76.8)	<0.001
Body mass index (kg/m^2)					
0-<23.3	74	31 (41.9)	57	39 (68.4)	0.003
>=23.3-<26.4	63	33 (52.4)	69	48 (69.6)	0.043
>=26.4-<30.4	54	23 (42.6)	78	49 (62.8)	0.022
>=30.4-<70.7	66	31 (47.0)	64	29 (45.3)	0.850

The adalimumab + MTX combination therapy showed superiority compared to MTX monotherapy on ACR50 response at Week 52 across all demographic subgroups except

subjects 65-74 and ≥ 75 years of age, non-Caucasians because the number of subjects was not sufficient to allow for meaningful conclusions.

Table 28. Modified Total Sharp Score at Week 52 by Subgroups

Modified Total Sharp Scores at Week 52	MTX (N = 257)			Adalimumab + MTX (N = 268)			p-value[a]
	N	Baseline (Mean)	Change from Baseline (Mean ± SD)	N	Baseline (Mean)	Change from Baseline (Mean ± SD)	
Sex							
Male	65	21.9	7.8 ± 13.1	75	17.9	1.1 ± 3.4	<0.001
Female	187	21.8	5.0 ± 12.6	193	18.2	1.4 ± 7.4	<0.001
Age (years)							
<40	43	20.7	5.2 ± 15.2	52	13.8	1.7 ± 5.8	0.014
40-64	164	18.2	6.3 ± 12.2	161	16.0	1.1 ± 7.1	<0.001
65-74	33	29.3	3.3 ± 13.2	42	29.4	1.4 ± 4.8	0.008
=>75	12	54.9	7.3 ± 9.7	13	25.6	2.0 ± 7.8	0.421
Race							
White	237	21.8	6.1 ± 12.4	250	18.9	1.1 ± 6.3	<0.001
Black	7	28.8	-3.1 ± 26.2	8	5.5	5.1 ± 9.3	0.857
Asian	1	13.5	3.0	6	9.4	7.0 ± 11.5	1.000
Other	7	19.1	3.4 ± 4.7	4	9.1	0.6 ± 0.9	0.564
Weight quartiles (kg)							
0 - <63	67	24.1	5.3 ± 13.5	55	20.7	1.2 ± 4.2	0.003
63 - <72.4	60	23.8	6.7 ± 12.9	69	21.6	2.4 ± 6.4	0.001
72.4 - <85	60	19.9	7.2 ± 12.8	67	16.7	1.0 ± 2.8	<0.001
=>85	65	19.5	4.0 ± 12.0	77	14.4	0.6 ± 9.6	0.004
Height quartiles (cm)							
0 - <160	54	24.3	7.7 ± 14.9	67	20.5	2.3 ± 6.9	0.009
160 - <165	61	21.0	5.2 ± 8.0	51	15.8	1.2 ± 3.3	0.001
165 - <173	68	21.2	2.0 ± 10.6	81	18.8	0.6 ± 9.2	0.007
=>173	69	21.3	8.3 ± 15.5	69	16.7	1.3 ± 3.5	<0.001
Body mass index (kg/m^2)							
0 - <23.1	69	25.5	7.4 ± 15.8	56	23.6	1.3 ± 3.4	<0.001
23.1 - <26.3	64	20.2	7.0 ± 13.8	69	20.8	2.2 ± 6.0	0.006
26.3 - <30.3	54	21.9	5.1 ± 8.1	77	14.8	1.1 ± 3.9	<0.001
=>30.3	65	19.5	3.3 ± 11.1	66	14.5	0.7 ± 10.4	0.029

The adalimumab + MTX combination therapy showed superiority compared to MTX monotherapy on modified TSS at Week 52 across all subgroups except subjects ≥ 75 years of age, non-Caucasians because the number of subjects was not sufficient to allow for meaningful conclusions.

4.2 Other Special/Subgroup Populations

Subgroup analyses of the primary efficacy endpoint were performed for baseline disease characters. The results are summarized in Tables 29 and 30.

Table 29. ACR50 Response at Week 52 by Subgroups (All Randomized Subjects)

	MTX (N = 257)		Adalimumab + MTX (N = 268)		
	N	n (%)	N	n (%)	p-value[a]
Duration of RA (years)					
0 - <0.5	138	65 (47.1)	156	98 (62.8)	0.007
0.5 - <1.0	37	15 (40.5)	42	26 (61.9)	0.058
1.0 - <2.0	42	19 (45.2)	41	23 (56.1)	0.322
2.0 - <3.0	36	17 (47.2)	27	16 (59.3)	0.344
>=3.0	4	2 (50.0)	2	2 (100.0)	0.759
CRP at Baseline					
Normal	18	8 (44.4)	32	12 (37.5)	0.857
Abnormal	239	110 (46.0)	236	153 (64.8)	<0.001
Previous DMARD use					
No	176	83 (47.2)	181	113 (62.4)	0.004
Yes	81	35 (43.2)	87	52 (59.8)	0.032
Rheumatoid factor at Baseline					
Positive	215	100 (46.5)	228	141 (61.8)	0.001
Negative	41	17 (41.5)	40	24 (60.0)	0.095
Corticosteroid use at Baseline					
No	166	81 (48.8)	172	107 (62.2)	0.013
Yes	91	37 (40.7)	96	58 (60.4)	0.007
Modified TSS at Baseline					
=0	5	0	16	11 (68.8)	0.030
>0	247	117 (47.4)	252	154 (61.1)	0.002
Erosion score at Baseline					
=0	11	2 (18.2)	20	11 (55.0)	0.108
>0	240	115 (47.9)	247	153 (61.9)	0.002
JSN score at Baseline					
=0	34	13 (38.2)	41	28 (68.3)	0.009
>0	217	104 (47.9)	226	136 (60.2)	0.010
Modified TSS at Baseline					
Missing	5	1 (20.0)	0	0	
>=0 - <6.25	57	18 (31.6)	73	42 (57.5)	0.003
>=6.25 - <14	60	35 (58.3)	64	47 (73.4)	0.076
>=14 - <26	57	33 (57.9)	74	39 (52.7)	0.554
>=26 - <149.5	78	31 (39.7)	57	37 (64.9)	0.004
Erosion score at Baseline					
Missing	6	1 (16.7)	1	1 (100.0)	0.608
0 - <3.5	55	22 (40.0)	68	38 (55.9)	0.080
>=3.5 - <8.5	54	27 (50.0)	76	54 (71.1)	0.015
>=8.5 - <16.5	70	40 (57.1)	65	32 (49.2)	0.357
>=16.5 - <98.5	72	28 (38.9)	58	40 (69.0)	<0.001
JSN score at Baseline					
Missing	6	1 (16.7)	1	1 (100.0)	0.608
0 - <1.5	62	22 (35.5)	64	41 (64.1)	0.001
>=1.5 - <4.5	55	28 (50.9)	69	43 (62.3)	0.202
>=4.5 - <10	62	34 (54.8)	74	45 (60.8)	0.482
>=10 - <84	72	33 (45.8)	60	35 (58.3)	0.152
Investigator Financial Interest[b]					
Yes	6	1 (16.7)	7	5 (71.4)	0.157
No	251	117 (46.6)	261	160 (61.3)	<0.001
Continent					
Australia	15	9 (60.0)	17	15 (88.2)	0.152
Europe	141	71 (50.4))	146	94 (64.4)	0.016
North America	101	38 (37.6)	105	56 (53.3)	0.024
TJC Quartiles					
0 - < 20	56	23 (41.1)	66	47 (71.2)	<0.001
>= 20 - < 30	64	30 (46.9)	76	48 (63.2)	0.053
>= 30 - < 41	70	39 (55.7)	61	34 (55.7)	0.998
>= 40 - < 68	67	26 (38.8)	65	36 (55.4)	0.056

CRP: c-reactive protein; DMARD: disease-modifying anti-rheumatic drug; JSN: joint space narrowing; RA: rheumatoid arthritis; TJC: tender joint count; TSS: Total Sharp score:a. P-value a chi-square test. b. Subgroup analysis based on the subjects enrolled at sites with *vs.* without a declared financial interest in Abbot.

Table 30. Modified Total Sharp Score at Week 52 by Subgroups

Modified Total Sharp Scores at Week 52	MTX (N = 257)			Adalimumab + MTX (N = 268)			p-value[a]
	N	Baseline (Mean)	Change from Baseline (Mean ± SD)	N	Baseline (Mean)	Change from Baseline (Mean ± SD)	
CRP at Baseline (mg/dL)							
<1.12	55	16.2	3.2 ± 7.5	71	13.0	2.0 ± 6.0	0.337
1.12 - <2.61	71	18.1	3.4 ± 8.6	66	16.1	0.5 ± 2.8	<0.001
2.61 - <5.61	66	27.2	4.2 ± 14.5	71	22.0	1.8 ± 5.7	0.002
=>5.61	60	25.5	12.5 ± 16.2	60	21.9	0.8 ± 10.1	<0.001
CRP							
Normal	18	16.8	2.0 ± 7.4	32	12.0	1.9 ± 5.7	0.755
Abnormal	234	22.2	6.0 ± 13.1	236	18.9	1.2 ± 6.6	<0.001
Previous DMARD use							
No	174	21.1	6.0 ± 12.8	181	17.8	1.6 ± 4.9	<0.001
Yes	78	23.4	5.1 ± 12.8	87	18.7	0.8 ± 9.0	0.003
Rheumatoid factor at Baseline[b]							
Positive	212	21.6	5.4 ± 12.8	228	17.6	1.2 ± 6.8	<0.001
Negative	39	23.0	7.5 ± 13.0	40	20.9	2.2 ± 4.8	0.038
Corticosteroid use at Baseline							
No	164	21.9	6.1 ± 12.9	172	18.1	1.7 ± 5.2	<0.001
Yes	88	21.8	5.0 ± 12.5	96	18.1	0.6 ± 8.4	<0.001
TSS Quartiles							
0 - <6	54	2.4	5.5 ± 10.7	66	2.7	1.6 ± 5.2	0.013
6 - <14	63	9.8	5.6 ± 12.1	71	8.9	1.6 ± 4.8	<0.001
14 - <26	56	18.5	7.9 ± 11.3	73	18.9	1.5 ± 4.9	<0.001
=>26	78	47.5	4.3 ± 15.4	57	46.4	0.2 ± 10.4	0.008
Financial Interest[c]							
Yes	6	39.2	10.2 ± 16.2	7	11.6	0.6 ± 1.5	0.347
No	246	21.4	5.6 ± 12.7	261	18.3	1.3 ± 6.6	<0.001
Continent							
Australia	15	14.9	8.0 ± 12.0	17	16.1	1.3 ± 1.8	0.072
Europe	139	21.6	5.3 ± 11.7	146	20.7	1.3 ± 7.6	<0.001
North America	98	23.2	6.0 ± 14.0	105	14.8	1.3 ± 5.4	<0.001
TJC Quartiles							
0 - < 20	56	18.3	4.2 ± 8.8	66	22.1	2.3 ± 5.4	0.008
>= 20 - < 30	61	24.9	2.9 ± 10.0	76	15.5	1.1 ± 9.9	0.016
>= 30 - < 41	69	19.8	8.0 ± 13.7	61	17.7	1.0 ± 4.5	<0.001
>= 41 - < 68	66	24.1	7.3 ± 15.8	65	17.5	0.8 ± 3.5	<0.001
Duration of RA (years)							
0 - <0.5	137	19.2	7.4 ± 13.2	156	15.1	1.8 ± 5.2	<0.001
0.5 - <1.0	36	20.1	4.3 ± 17.4	42	19.8	1.5 ± 5.0	0.077
1.0 - <2.0	40	22.5	4.7 ± 11.1	41	19.4	0.9 ± 4.3	0.006
2.0 - <3.0	35	32.9	2.3 ± 4.9	27	26.5	-0.9 ± 14.3	0.943
>=3.0	4	26.5	2.6 ± 2.7	2	73.0	-1.5 ± 0.7	0.166

CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis; TJC: tender joint count; TSS: Total Sharp score

a. P-value is from the Mann Whitney U test comparing MTX monotherapy and adalimumab + MTX combination therapy.

b. Positive = ≥ 20 IU/mL

c. Subgroup analysis based on the subjects enrolled at sites with *vs.* without a declared financial interest in Abbott.

The adalimumab + MTX combination therapy showed superiority on ACR50 response and modified TSS at Week 52 compared to MTX monotherapy across most subgroups. In

some subgroups, such as certain x-ray parameter categories, and subjects enrolled at sites with a financial interest in Abbott, the population size was not sufficient to allow for meaningful conclusions.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The higher percentage of dropouts from the placebo group than the treated groups was observed mainly due to lack of efficacy. The reviewer used the partial imputation method as sensitivity analyses for the co-primary efficacy endpoints to create the similar drop-out rates among three treatment groups, so that the sample distribution of the follow-up time in the three arms become equal and dependence between response variable and the drop-out process in the three groups are equal (Lynn Wei and Weichung J. Shiu, 2001). The sponsor performed two sensitivity analyses using all data as observed without imputation for missing data (considered as non-responders) and the last observation carried forward (LOCF) approach for ACR50 response. The results of the sponsor's sensitivity analyses and the partial imputation were robust. The result of reviewer's GEE analysis the proportion of ACR50 responses as a supportive analysis also confirms the results of primary analysis.

The sponsor's four sensitivity analyses of the statistical analysis on change from Baseline in Modified TSS at Week 52 (Table 14) analyzing data as observed (*i.e.*, completer population) and using the LOCF approach, an ANOVA model, and 75th percentile for subjects missing Baseline or Week 52 x-rays were robust. The results of reviewer's partial imputation approach are also consistent.

5.2 Conclusions and Recommendations

Base on the results of the analysis of both primary endpoints, the proportion of subjects who achieved anACR50 response and the change from Baseline in modified TSS following 52 weeks of treatment, demonstrated that adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy in improving signs and symptoms and inhibiting progression of radiographic progression in subjects with recently diagnosed moderate to severe RA.

All of the major secondary endpoints supported the statistical superiority of adalimumab + MTX combination therapy compared to MTX monotherapy with the exception of the last, the mental component of the SF-36® at Week 52.

Adalimumab + MTX combination therapy was found to be clinically and statistically superior to MTX monotherapy in improvement of physical function, improvement of signs and symptoms, inhibition of radiographic progression, achievement of clinical remission as defined by DAS28 <2.6, improvement in the physical aspect of QoL, and achievement of a major clinical response defined as an ACR70 response for six continuous months. For the mental component of the SF-36®, adalimumab + MTX

combination therapy was not shown to be statistically significantly better than MTX monotherapy.

In other secondary analyses results that the sponsor performed, Adalimumab + MTX combination therapy is clinically and statistically superior to MTX monotherapy and adalimumab monotherapy in the physical aspect of QoL, as demonstrated by the physical component of the SF-36® over 104 weeks of treatment.

Overall, the use of adalimumab 40 mg eow + MTX $\leq$ 20 mg/week combination treatment shows the benefit of improvement in signs and symptoms, inhibition of radiographic progression, improvement of physical function, induction of major clinical response and remission, overall high rate of low disease activity achieved, and acceptable safety profile for the treatment of subjects recently diagnosed with moderate to severe RA.

References

Lynn Wei and Weichung J. Shih. Partial imputation approach to analysis of repeated measurements with dependent drop-outs. Statistics in Medicine 2001; 20:1197-1214.

SIGNATURES/DISTRIBUTION LIST PAGE

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

OTHER REVIEW(S)

07/20/05

DIAGNOSTIC IMAGING REVIEW

Application Type	**sBLA**
Submission Number	**STN 125057 / 46**
Submission Code	**N/A**
Letter Date	**December 17, 2004**
Stamp Date	**December 20, 2004**
PDUFA Goal Date	**October 20, 2005**
Review Completion Date	**June 29, 2005**
Reviewer Names	**H. W. Ju, M.D.** **Lydia Martynec, MD**
Through	**George Mills, MD** **Director, Medical Imaging** **Jeffrey Siegel, MD** **Team Leader** **Alex Gorovets, MD** **Clinical Reviewer**
Established Name	**HUMIRA (adalimumab)**
Therapeutic Class	**Anti-TNFα Antibody**
Applicant	**Abbott Labs**
Priority Designation	**Standard Application**
Formulation	**Subcutaneous Injection**
Dose Regimen	**40 mg EOW**
Indication	**Early Rheumatoid Arthritis**
Intended Population	**Adult Patient with Early Rheumatoid Arthritis**

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation on Approval

Recommend approving the sBLA with the proposed label

8 ADDITIONAL CLINICAL ISSUES

8.1 Reason for Consult

This consultation is requested to perform an analysis of the imaging dataset (Joint Radiographs of hands and feet) submitted to the sBLA. This review is to perform a quality check on the images submitted for completeness and an image review of 180 subjects identified by the statistician and clinical and imaging reviewers.

8.1.1 Clinical Study

Adalimumab was licensed by Abbott on December 31, 2002 for the treatment of patients with moderate to severely active early rheumatoid arthritis.

Protocol DE013 was a prospective, multi-center randomized, double-blind, active comparator-controlled, parallel-group study comparing the fully human monoclonal anti-TNFα antibody adalimumab given every second week with methotrexate (MTX) given weekly and the combination of adalimumab and methotrexate administered over 2 years in patients with early Rheumatoid Arthritis, RA (defined as RA meeting the American College of Rheumatology (ACR) criteria and disease duration of less than 3 years). There were 799 subjects randomized in the study. Subjects were randomized 1:1:1 to one of three treatment groups: adalimumab 40 mg every other week (eow), adalimumab 40 mg eow together with weekly MTX (≤ 20 mg/wk), or weekly MTX (≤ 20 mg/week). The clinical objective was to assess the efficacy of adalimumab + MTX combination therapy vs. MTX monotherapy in 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, including recently diagnosed patients who have not been previously treated with MTX . The radiological objective was to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression of structure damage. This report will focus on the radiographic endpoints of the study.

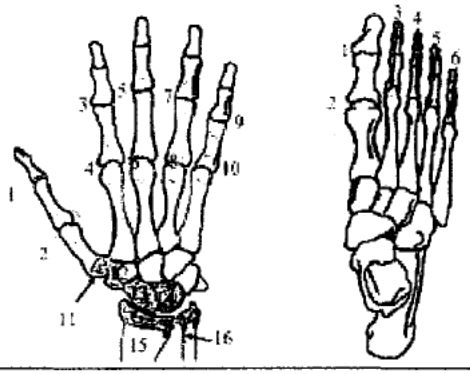
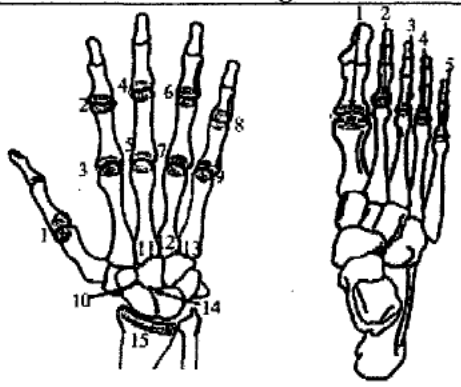
8.1.2 Description of Scoring System

The radiological objective was to investigate whether adalimumab + MTX combination therapy was superior to MTX monotherapy in the inhibition of radiographic progression as measured by change from Baseline in modified Total Sharp Score (TSS) at weeks 52 and 104 and change from Baseline in components (erosion and joint space narrowing

scores) of the modified TSS at Weeks 52 and 104. The Erosion scores and Joint Space Narrowing (JSN) Scores for each reader were calculated and the mean scored derived. The final Total Sharp Score was defined as the sum of the Erosion and JSN scores. The readers used a modified Sharp method to score the joints of both hands and feet. The original Sharp method scored 27 joints of each hand-wrist for erosion and joint space narrowing. In 1985, the Sharp method was revised to score 17 joints of each hand-wrist for erosion and 18 points for joint space narrowing. Radiographs in this study were assessed by the modified version of the Sharp method as follows:

Erosion score was recorded for each hand/writs (16 joints: 4 PIP joints, 6 MCP/IP joints, and 6 wrist joints) and each forefoot (6 joints: 5 PIP and 1 IP joints) on a 6 point scale (0 = no erosions; 1= 1 discreet erosion or <= 21% joint involvement; 2 = 2 discreet erosions or 21 – 40% joint involvement; 3= 3 discreet erosions or 41 – 60% joint involvement; 4 = 4 discreet erosions or 61 - 80% joint involvement; 5 = extension destruction with > 80% joint involvement). Joint space narrowing was recorded for each hand/wrist (15 joints: 4 PIP joints, 5 MCP/IP joints and 6 wrist joints and forefoot (5 PIP joints) on a 5-point scale (0 = no narrowing; 1 = up to 25% narrowing; 2 = 26-65% narrowing; 3 = 66-99% narrowing; 4 = complete narrowing). To determine the modified TSS for each subject, the total erosion score (scale 0-230) and the joint space narrowing score (scale 0-168) were added (TSS score scale 0-398).

The following diagrams demonstrate the anatomical structure of the joints of the hand and foot for Erosion Scoring and Joint Space Narrowing and modified Sharp Scoring system respectively:

The Joints for Erosion Scoring	The Joints for JSN Scoring
	

Hand

1	1st IP	11	MC1	1	1st IP
2	1st MCP	12	Mul	2	1st MTP
3	2nd PIP	13	Nav	3	2nd MTP
4	2nd MCP	14	Lunate	4	3rd MTP
5	3rd PIP	15	Radius	5	4th MTP
6	3rd MCP	16	Ulna	6	5th MTP
7	4th PIP				
8	4th MCP				
9	5th PIP				
10	5th MCP				

The Modified Sharp Scoring Criteria:

0 - No erosion
1 - One discreet erosion or involvement of less than 21% of the joint area by erosion
2 -Two discreet erosions or involvement of 21 through 40% of the joint
3 - Three discreet erosions or involvement of 41 through 60%% of the joint
4 - Four discreet erosions or involvement of 61 through 80 % of the joint
5 - Extension destruction involving more than 80%

Invaluable Joint Scores:

C - Surgery/Joint Replacement
D - Subluxation/Superimposition
E - OA or Other Arthritis
F - Radiographically Inadequate

Hand

1	1st MCP	10	M - NA	1	1st MTP
2	2nd PIP	11	CMC3	2	2nd MTP
3	2nd MCP	12	CMC4	3	3rd MTP
4	3rd PIP	13	CMC5	4	4th MTP
5	3rd MCP	14	CAPN	5	5th MTP
6	4th PIP	15	Radius		
7	4th MCP				
8	5th PIP				
9	5th MCP				

The Modified Sharp Scoring Criteria:

0 – No Narrowing
1- Asymmetrical and or minimal narrowing – up to 25%
2 – Definite narrowing with loss of up to 65% of the normal space
3 – Definite narrowing with loss of 65 to 99% of the normal space
4 – Absence of a joint space

Invaluable Joint Scores:

C - Surgery/Joint Replacement
D - Subluxation/Superimposition
E - OA or Other Arthritis
F - Radiographically Inadequate

8.1.3 Independent Reader Procedure

The independent review of radiographs for protocol DE013 was conducted by (b) (4), an independent Contract Research Organization. The clinical trial sites followed a standardized imaging manual developed by (b) (4) and forwarded the images to (b) (4) for data processing and preparation for the independent readings. The independent readers performing evaluations for Protocol DE013 were

trained at a training session conducted by [redacted]. Four readers participated in the training session on May 9. 2003. The four readers were [redacted], and [redacted]. The objectives of the independent imaging review were:

- To evaluate the radiographic changes due to Adalimumab given every second week, methotrexate given weekly , and the combination of adalimumab and methotrexate administered of 2 years in patient with early rheumatoid arthritis
- To evaluate the damage to joints using serial radiographic of the hands and feet
- To assess the extent of damage with separate scores for erosions and joint space narrowing using a modified Sharp method, and the Total Sharp Scores.

The protocol specified that each patient was to have posteroanterior radiographic examinations of the both hands and feet recorded on film at Baseline Week 26, Week 52, and Week 104, or at the last visit for any subject who terminated participation prior to Week 104. It was intended that all hand and foot radiographs were obtained using (mammography grade) single emulsion film and single fine screen cassettes that are matched to the film for color and speed. Prior approval by [redacted]; was required for sites using digital radiography equipment or sites unable to accommodate the type of film and cassettes provided for this study. The original films were digitized and stored electronically by [redacted]; for blinded reading. Both the subject and the study physician remained blinded to the medication for these evaluations.

The two paired readers (selected from the 4 trained readers at [redacted]) who performed the independent reading were presented each patient's case using an independent reading system. This independent reading system, referred to as a remote [redacted] and consists of an image display system with two high resolution monitors to view the image data set and a data entry screen with a single monitor which contains a computerized score sheet incorporating the modified Sharp Scoring Method. The [redacted] presented to each reader the image sets for each patient in the following order: right hand-wrist and foot and then left hand-wrist and foot. There were two to four time points for each image set. The order of the time points was randomized by [redacted] based on specifications provided by Abbott. The readers first viewed the image set (i.e., right hand-wrist and foot at each time point) on one monitor to get an overview of the extent of joint damage. The reader would score the absence or presence of 5 radiographic features associated with RA. The reader was then presented with a strip of joints from each cropped image of the image set in a randomized sequence. The reader could indicate that all joints on a strip are normal and move to the next strip and the [redacted] would enter zero on the computerized scoring sheet for all of the joints on that strip. If a joint was eroded or narrowed or unreadable for erosions or JSN due to image quality or technique, presence of disease other than RA, or presence of damage due to RA, the reader would score each joint on the strip for erosions and JSN or indicate why the joint could not be read. These scores were entered directly onto the electronic score sheet. The reader would continue until all of the strips for a given set have been read. The reader

would indicate that the scoring was completed at the end of each image set. An image could not be re-scored after the reader indicated that he had completed the scoring. The reader was instructed to complete the patient case (all image sets) before going to the next case or before quitting the reading session. During the reading session, the (b) (4) program would store images of the screens (screen-shots) that the reader completed so that the data on the electronic score sheets could be verified. The data from the electronic score sheet was sent to (b) (4) where it was translated into a SAS data set and sent to Abbott to be merged with the clinical database.

Abbott has submitted the radiographic data set base as part of the BLA, which is the scope of this review.

The consult is requested to perform an analysis of the imaging dataset (Joint Radiographs) submitted to the BLA. The reviewer is asked to perform a quality check on the images submitted for completeness and perform an image review of 180 patients identified by the clinical reviewer and the statistician.

The sponsor has not submitted specific questions regarding the radiographic review to the reviewer.

8.14 Financial Disclosure

The sponsor provided financial disclosures of readers who had performed the independent reader assessment for the study. The financial disclosure form for the 4 blinded readers has been submitted with no apparent conflict of interest noted.

8.2 Description of the Material Provided for Review.

The sponsor has submitted a 2 Year Image Database for protocol DE013. The image database contains a hard drive that contains digitized radiographs for patients enrolled in this protocol.

Seven hundred ninety nine (799) subjects enrolled into the 2 year study of Protocol DE013. The following table summarized the number of subjects with radiographs by visit.

Number of Subjects with X-ray Data by Visit

Total Sharp Score	Treatment Group	Baseline	Week 26	Week 52	Week 104	Early Termination
Available	Adalimumab	271	230	205	166	45
	Adalimumab + MTX	267	241	230	203	31
	MTX	251	219	205	173	45
Missing	Adalimumab	3	44	69	108	
	Adalimumab + MTX	1	27	38	65	
	MTX	6	38	52	84	

The Imaging Database was successfully loaded by the [redacted] (b) (4) representative on January 7, 2005.

8.3 Consultant's Review of Radiographic Dataset

The reviewer was able to open the full imaging dataset consisting of all images from the 799 subjects. The number of these subjects included subjects with missing images at baseline, week 26, week 52, and week 104 as indicated in the above table.

Alex Gorovets, M.D., the clinical reviewer on the file, requested the review of the images for subjects based on the following criteria:

- Adalimumab + MTX: Subjects with the least x-ray progression from baseline; i.e. comparing with the baseline values, the patients remain almost stable.
- Adalimumab alone: Similar to the above criteria, subjects with the least x-ray progression from baseline.
- MTX alone: Similar to the above criteria, subjects with the least x-ray progression from baseline.
- MTX alone: Differ from the above criteria, subjects with the most x-ray progression from baseline.

In consultation with Kyung Y. Lee, PhD, FDA statistician, the following images were selected:

Adalimumab + MTX	Adalimumab	MTX (Least change)	MTX (Worst Progression)
#01209	#00403	#02507	#00103
#03115	#02205	#03606	#02809
#03654	#03704	#07004	#03707
#04804	#06304	#09902****	#09406+
#06308	#09005	#12610	#11115
#08208	#10107*		
#10001	#10408		
#10813	#11513*		
#11519*	#11809		
#16303	#16310****		

* Missing baseline images
**** Missing week 104 images
\+ Reader 2 did not provide readings on right hand and both feet

The reviewers (Drs. Martynec and Ju) were able to validate the reading score of the independent readers for all of the subjects for whom review was requested.

Radiographs from an additional 150 subjects were also reviewed. The subject radiographs for the review were chosen randomly by the reviewers. The selected subjects included subjects with missing images at baseline (1 subject) and week 104 (4 subjects). The radiographs that were reviewed for the 150 subjects are listed below:

Adalimumab + MTX (Subjects 00101 – 07603)		**Adalimumab ONLY (Subjects 07701-19002)**		**MTX ONLY (Subjects 00101-19002)**	
#00106	#03815	# 07704	#11113	#00211	#08510
#00504	#04101****	# 07808	#11119	#01102	#09104
#00506****	#04301	#08207	#11121	#01911	#09304
#00803	#04408	#08302	#11220	#02101	#09403
#01202	#04411	#08404****	#11408	#02624	#10102
#01601	#04707	#08503	#11412	#02808	#10209
#01903	#05201	#08602	#11523	#03203	#10510
#01917	#05204	#08902	#11529	#03403	#10607
#02108	#05303	#09103	#11535	#03622	#10907
#02303	#05608	#09301	#11601	#03646	#11004
#02606	#05905	#09307	#11809	#03652****	#11123
#02701	#06001	#09503	#12104	#03902	#11407
#02814	#06009	#09602	#12409	#04501	#11528
#03102	#06013	#09606	#12413	#04414	#11805
#03205	#06101	#09904	#12602	#05003	#12001
#03211	#06217	#10110****	#12613	#05208	#12416
#03302	#06228	#10116	#13001	#05612	#12608
#03405	#06309	#10207	#13302	#06006	#13301
#03609	#06508	#10410	#14603	#06023	#13502
#03616	#06703	#10514	#15006	#06212	#15010
#03625	#06714	#10603	#15013	#06226	#16002
#03626*	#06805	#10801	#15301	#06507	#16312
#03639	#06903	#10807	#16005	#06803	#18003
#03655	#07306	#10905	#18001	#07402	#18101
#03803	#07701	#11003	#18103	#08201	#19002

* Baseline image only
**** Missing image week 104

In assessing inter-reader variability, only minor differences in scoring interpretation was noted. The reviewer was able to validate the reading score of the independent reader for all of the patients reviewed. The majority of scoring differences in scoring were one point between the two readers for the studies reviewed.

The radiographic datasets for each subject at all protocol required time points were assessed by the agency reviewer. The following deficiencies were observed.

8.4 Deficiencies

The reviewers noted minor quality control issues as described below.

8.4.1 Minor Protocol Violations

- Artifacts
  Scratch marks: Subject #00403
  Dirty film: Subject #01102

- Technician Initials included in the Radiographs
  Subjects #01209 and #00211

- Radiographs obtained with inappropriate markers
  Subject #03654: "P" was used for the right marker (instead of the "R" for right marker)
  Subject #02808: "G" was used for both right left markers (instead of "R" and "L" for right and left markers respectively
  Subject #09503: "SIN" was used for left marker (instead of "L" for left marker)
  Subject #09606: "DX" was used for right marker (instead of "R" for right marker)

- Radiographs obtained without removing jewelry from the hand
  Subjects #02303, #05201, #06805, and #11412

8.4.2 Discrepancy between the Agency Reviewer and Independent Reader Radiograph Assessment

For each subject : (1) refers to the agency reviewer assessment
(2) refers to the independent reader assessment

Subject #02809: (1) Right hand has generalized bone erosion on PIP 2, 3, and 4
(2) Both readers scored PIP2 as normal and PIPs 3, 4 and 5 as abnormal

Subject #03302: (1) MCP2 of both hands are normal
(2) Both readers scored bone erosion

Subject #03803: (1) PIP3 of right hand was abnormal and PIP4 of right hand was normal
(2) Both readers read PIP3 as normal and PIP4 as abnormal

Subject #06226: (1) PIP5 of left hand is normal
(2) Both readers scored PIP5 of left hand as bone erosion

Subject #06703: (1) PIP4 of right hand and PIP4 of left hand are normal
(2) Both readers scored PIP4 of right and PIP4 of left hand as an erosion

Subject #08503: (1) MCP3 of right hand is abnormal and MCP2 of right hand is normal
(2) Both readers read MCP2 of right hand for erosion and MCP3 of left hand as normal

Subject #09606	(1) MCP3 of right hand appears normal (2) Both readers scored MCP3 of right hand for bone erosion
Subject #11113:	(1) MCP3 of left hand is normal and MCP2 of left hand is abnormal (2) Both readers read MCP3 for erosion and MCP2 as normal
Subject #15006	(1) PIP2 and PIP 3 of right hand have severe bone erosion and PIP4 of right hand is normal (2) Both readers read PIP3 and PIP4 of right hand for severe bone erosion and PIP2 of right was scored 0 and 1 respectively
Subject #15013:	(1) PIP3 of left hand and PIP4 of right hand appear normal (2) Both readers scored PIP3 of left hand and PIP 4 of right hand for erosion
Subject #18003:	(1) PIP4 of right hand is normal and PIP3 of right hand has severe bone erosion (2) Both readers read PIP3 as normal and PIP4 severe bone erosion.

9. OVERALL ASSESSMENT

9.1 Conclusion

In conclusion, in the performance of the quality check of the 180/799 subject (22.5%) the radiographic data sets (30 subjects identified by the clinical reviewer and statistician and an additional 150 subjects randomly selected by the reviewer) the reviewers were able to validate the reading score of the independent reading score for all of the subjects queried.

In addition, the cited minor protocol violations, artifacts and minor inconsistencies between the agency reviewer and the independent reader score did not affect the evaluation of the radiographic data set for efficacy.

9.2 Recommendation on Regulatory Action

The submitted radiographic database supports the approval of adalimumab for the proposed indication - use in adult patients with early rheumatoid arthritis.

H. W. Ju, M.D.
H. W. Ju, MD
Medical Officer
HFD-107

George Mills, MD
Division Director
HFD-160

Patricia Keegan 1/20/05
Patricia Keegan, MD
Division Director
HFD-107

Lydia O. Martynec
Lydia Martynec, MD
Medical Officer
HFD-107

Joseph E Gootenberg
Joseph Gootenberg, MD
Team Leader
HFD-107

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/46

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

020805

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 125057/46 and 125057/(b) **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 1/17/05 **Action Date:** October 20, 2005

HFM 109 **Product and Proprietary names/dosage form:** Adalimumab, Humira, prefilled syringe, dosage strength (b) (4))

Applicant: Abbott Laboratories **Therapeutic Class:** N/A

Indication(s) previously approved:
12/31/02 BLA - reducing signs and symptoms and inhibiting the progression of structural damage n adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs
7/30/04 Efficacy supplement - expand the indication to include improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDS

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: 125057/46: to include recently diagnosed patients with moderately to severe RA who have not received methotrexate
125057/(b): (b) (4)

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☑ **No: Please check all that apply:** ☐ **Partial Waiver** ☑ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☑ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
Other: awaiting results of ongoing studies in (b) (4) (b) (4)
Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:
Beverly Conner 1/28/05
Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

telecon

Teleconference Memorandum

Date:	09-27-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Erik Laughner
Re:	Adalimumab
STN:	125057.46 and 125057.58 and 125057.45

Discussion:

Left voicemail message with Jim Steck that the Agency was ready to receive a (b)(4) Humira label reflective of the 3 separate supplements for 125057.46, 125057.45, and 125057.58. The Sponsor was to submit the (b)(4) label as a secure email with clear demarcations of any editorial changes. After the Agency agreed to this version, the Sponsor could then immediately send in the final labeling for Agency action.

Telecon.092005

Teleconference Memorandum

Date:	09-20-05
Sponsor Participants:	Jim Steck and John Perez, M.D. / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Introduction:

The patient narrative for subject 1307001 who developed a lupus like syndrome after 259 days on adalimumab monotherapy indicated that the outcome was "Not Resolved".
However, the sponsor proposed to revise the labeling (b) (4) to indicate that two patients developed lupus-like syndrome and "patients improved following discontinuation of therapy", (b) (4)
FDA requested additional information. The sponsor e-mailed a copy of the questionnaire.
According to the questionnaire provided by the sponsor, dated "13-7-05", that includes the answers from the investigator, patient's condition did not worsen, patient was not diagnosed with lupus during the additional diagnostic evaluations, and the event of "lupus-like syndrome" resolved. The date of "Resolve" was listed as 10-02-03; the event date was 15-Mar-02.

Discussion:

Abbott confirmed the content of the questionnaire and will submit a formal amendment.
Abbott will further amend the proposed labeling revision to update the number of patients treated with HUMIRA listed in the Autoantibodies section of the labeling from 2334 to 3046.

Telecon.090805

TELECON MEMO

Date: September 8, 2005

Sponsor Participants: Tom Harris, Senior Director Global Pharmaceutical Regulatory Affairs (GPRA), Immunology Regulatory
John Medich, Global Project Head, Humira Global Pharmaceutical Research and Development (GPRD), Immunology Clinical
John Perez, Associate Medical Director GPRD, Immunology Clinical
Jim Steck, Director, GPRA, US Area Regulatory
Erik von Borcke, General Manager, Immunology, Pharmaceutical Products Division Commerical
FDA Participants: Jeff Siegel; Alex Gorovets, Erik Laughner

STN: 125057.46 and 125057.58

Response to Abbott Counter-Revisions

FDA orally presented the responding comments:

HUMIRA LABELING

Outstanding issues as of 08-25-05

1. In response to the FDA request, Abbott expanded Table 5 to include HUMIRA monotherapy data and all data at week 104. Abbott presented the following:

Table 5: Radiographic Mean Change (b) (4) in Study V

(b) (4)

(b) (4)

(b) (4)

[redacted]

Our recommendations are to revise the heading to read: "Radiographic Mean Change* in Study V",

- present the Week 52 data above the Week 104 data

(b) (4)

[redacted]

(b) (4)

[redacted]

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Laughner, Erik

From: Hoyt, Colleen
Sent: Thursday, August 25, 2005 4:25 PM
To: Laughner, Erik
Subject: RE: Compliance check needed for BLA 125057/46; abbott; adalimumab

RE: Request for compliance che...

Erik - there have been no changes in the compliance or enforcement status of the firms listed in the compliance check request since I issued the initial response on 5/16/05. Please refer to the 5/16/05 compliance check response attached.

Thanks-

Colleen

-----Original Message-----
From: Laughner, Erik
Sent: Tuesday, August 16, 2005 8:58 AM
To: Hoyt, Colleen
Subject: Compliance check needed for BLA 125057/46; abbott; adalimumab
Importance: High

Hi Colleen,

I have an efficacy supplement 125057_46 which is nearing completion. Li Jianming had performed an early review for CE/EA and at the same time requested a compliance check. However, the 60 day clock has expired and I need to have it re-checked. Attached, you will find a pdf of the sites for review.

Thank you,

Erik Laughner, RPM
ODEVI

Laughner, Erik

From: Laughner, Erik
Sent: Tuesday, August 16, 2005 8:58 AM
To: Hoyt, Colleen
Subject: Compliance check needed for BLA 125057/46; abbott; adalimumab

Importance: High

SFX97C.pdf (53 KB)

i Colleen,

I have an efficacy supplement 125057_46 which is nearing completion. Li Jianming had performed an early review for CE/EA and at the same time requested a compliance check. However, the 60 day clock has expired and I need to have it re-checked. Attached, you will find a pdf of the sites for review.

Thank you,

Erik Laughner, RPM
ODEVI

Telecon.081105

TELECON MEMO

Date: August 11, 2005

Sponsor Participants: Tom Harris, Senior Director Global Pharmaceutical Regulatory Affairs (GPRA), Immunology Regulatory
John Medich, Global Project Head, Humira Global Pharmaceutical Research and Development (GPRD), Immunology Clinical
John Perez, Associate Medical Director GPRD, Immunology Clinical
Silvia Pfaff, Director, GPRA, Immunology Regulatory
Jim Steck, Director, GPRA, US Area Regulatory
Erik von Borcke, General Manager, Immunology, Pharmaceutical Products Division Commerical
Karen Walles, Manager, GPRA, Advertising and Promotion Regulatory

FDA Participants: Jeff Siegel; Alex Gorovets

Abbott presented the contents of the following document e-mailed to FDA on 08-10-05, and FDA presented the responding comments (in red italics):

Response to FDA Labeling Revisions
Rationale for Abbott Counter-Revisions

This document provides the data requested in FDA's revisions to our labeling draft submitted in our pending efficacy supplement (125057/46) and labeling supplement (125057/58) for Humira® (adalimumab). The Sponsor finds acceptable most of the Agency's changes contained in the versions e-mailed to Abbott on August 1, 2005. However, this document also includes some counter-revisions proposed by Abbott with the corresponding rationale.

We would like to discuss the counter-proposals in our teleconference scheduled for August 11, 2005. We have provided a marked-up version of the labeling for your review with the Abbott additions and counter-proposals highlighted in yellow.

The Abbott proposals for each change are also summarized below by: Labeling Section, Topic, and Line Number.

CLINICAL STUDIES

Radiographic Data Presentation

LINES: 212-224

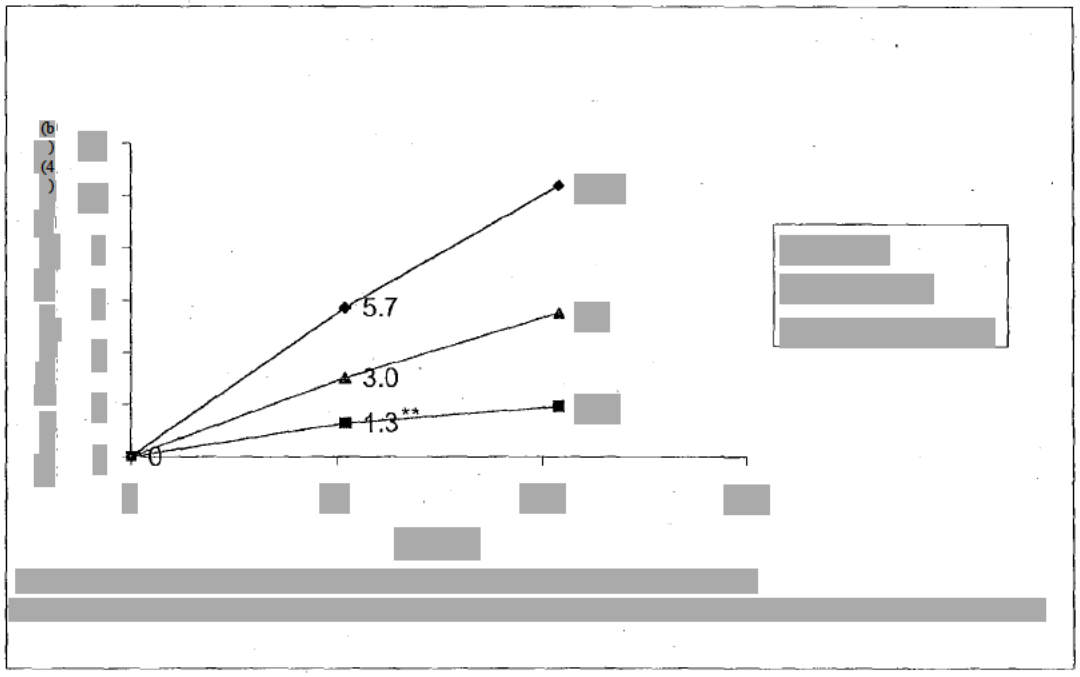
Upon receiving the request from FDA to provide the HUMIRA monotherapy data and the Week 104 data and p values in this section, Abbott has considered how best to present

these data and proposes to (b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

(b) (4)

Other Edits to the Clinical Studies Section:

(b) (4)

Line 192: Table 3 has been expanded as requested to include the HUMIRA monotherapy data with corresponding p-values.

Noted and agreed.

WARNINGS AND ADVERSE REACTIONS

Malignancies:

LINES: (b) (4)

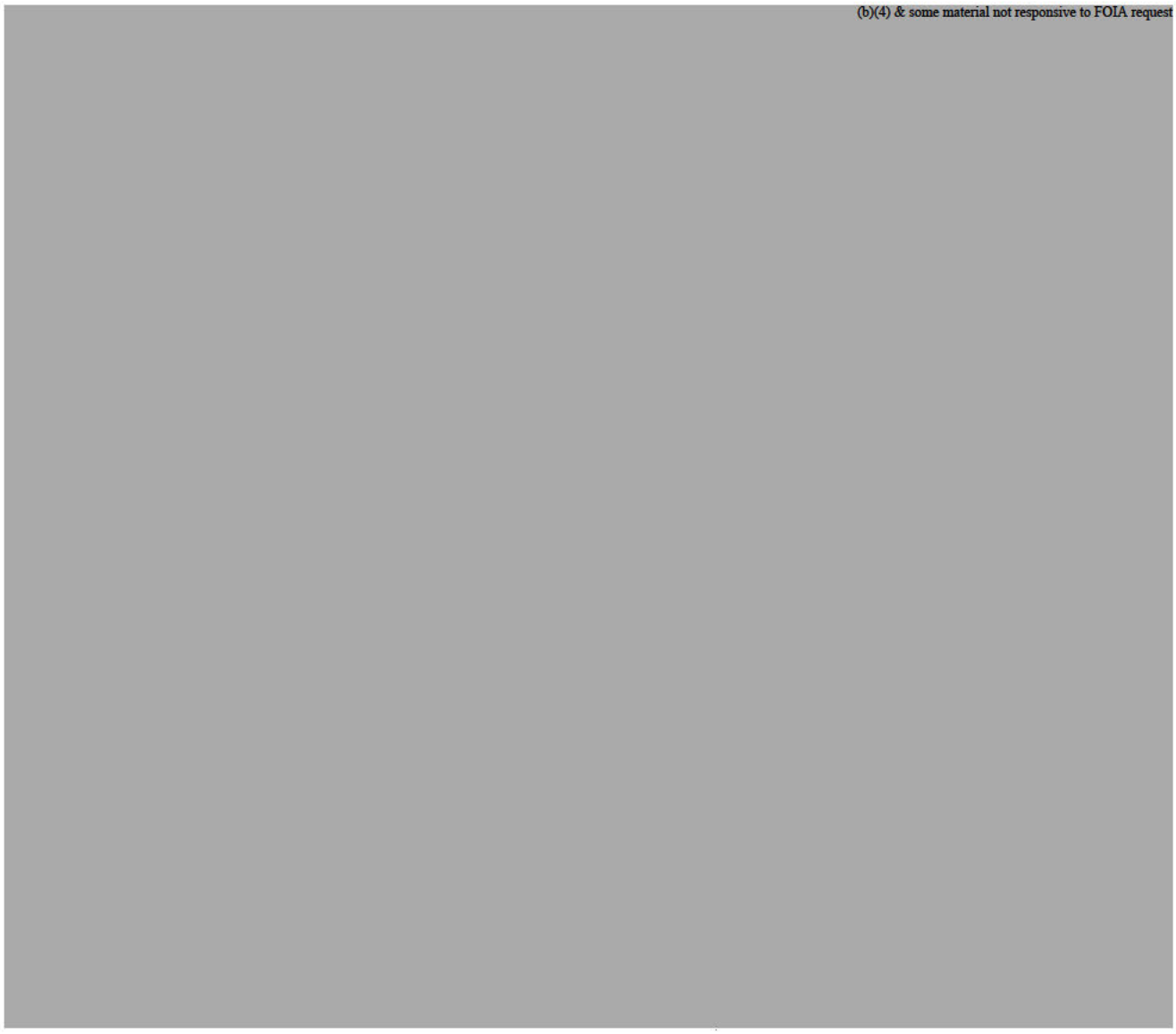
(b) (4)

(b) (4)

Non-melanoma skin cancer

On Lines 307 to 311 the Agency also recommended that Abbott provide the non-melanoma skin cancer rates in the controlled portion of these trials. We agree with adding these data to the prescribing information.

(b) (4)



BOX WARNING AND WARNINGS
Tuberculosis:

We have noted and agree with the FDA changes to the HUMIRA box warning (Lines 10 to 29).

(b) (4)

(b) (4)

ADVERSE REACTIONS

Other Safety Edits

Starting on Line 557 in the section in Adverse Reactions on Autoantibodies, we have modified wording to include a case (i.e. two cases total for HUMIRA clinical database) of clinical signs suggestive of new-onset lupus-like syndrome that was submitted in the clinical study report for Study DE013 (See Section 12.3.1.3.4: patient number 13-07001). This should have been indicated in our original labeling proposal and we have now adjusted this section accordingly.

Noted and agreed

Following the above discussion the sponsor communicated an agreement with the comments by the FDA and will resubmit the revised labeling.

64 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Telecon

Teleconference Memorandum

Date:	08-04-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

FDA requested to clarify how many subjects in each treatment group had a decrease in the dosing interval of Adalimumab from "eow" to weekly. The decrease in the dosing interval was allowed if a subject failed to achieve an ACR20 by Week 16.

The sponsor responded that in the Adalimumab monotherapy group 41 subjects had their dosing interval decreased, 17 in the combination group, and 37 for the placebo dosing in the MTX monotherapy group.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 4, 2005

TO: Erik Laughner, Regulatory Project Manager
Alex Gorovets, M.D., Clinical Reviewer
Division of Division of Retroviral and Monoclonal Antibody Drugs, HFD-108

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Dianne D. Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

BLA: #125057/46

APPLICANT: Abbott Laboratories

DRUG: Humira (adalimumab)

CHEMICAL CLASSIFICATION: 1S

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of early rheumatoid arthritis

CONSULTATION REQUEST DATE: February 16, 2005

ACTION GOAL DATE: September 20, 2005

PDUFA DATE: October 20, 2005

I. BACKGROUND:

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. It is a progressive illness that ultimately causes joint destruction, and significant disability. It is more common in women than in men, and the incidence increases with age. The disease is characterized by a progressive inflammatory arthritis manifested by symmetrical polyarticular joint swelling and tenderness.

Early in the disease process pain is the main contributor to loss of function. With disease progression joint space narrowing and bony erosion account for additional loss of function. Based on findings of the Early

Rheumatoid Arthritis (ERA) trial there is scientific support for early intervention with anti-tumor necrosis factor (TNF) monotherapy in patients with RA. Early RA is defined as disease of less than three years duration.

The current study differs from previous studies in that subjects did not have to be DMARD (disease-modifying, anti-rheumatic drug) failures in order to participate, and that subjects with RA of <1 year duration were enrolled. The objective was to prove that early intervention could have a significant positive effect on disease progression. Previous early RA trials have compared MTX to TNF monotherapy (ERA) or to combination therapy only (ASPIRE).

There were three arms to the study: adalimumab 40 mg every other week (eow) + methotrexate (MTX) ≤ 20mg/week, adalimumab 40 mg eow, or MTX ≤ 20 mg/week. There was no placebo arm. ACR 50 response at Week 52 was chosen as the primary endpoint for the reduction of signs and symptoms. Change from baseline in the modified Total Sharp Score (TSS) at Week 52 was chosen as the conditional primary efficacy endpoint to assess the inhibition of radiographic progression in RA subjects.

The sites were chosen for their high enrollment. The medical officer had no special concerns about data integrity at any of the sites. Dr. (b) (4) is a high volume researcher. He has 79 studies listed in the Clinical Investigator System databank. He was inspected in 1998 and classified VAI for inadequate consent and failure to report Adverse events. Dr. (b) (4) has 8 studies listed. He has no prior inspections.

Objective measures of efficacy were X-rays of hands and feet visit 1 (week -4) and visit 14 (week 52) and C- reactive protein (CRP) performed monthly, at each study visit. Tender and swollen joint counts, though time-consuming, were efficacy assessments that had to be performed at each visit. Further assessments were morning stiffness measured in minutes and averaged over the week prior to the visit. Other measures were patient and physician assessment of disease activity, and a patient assessment of pain. All three assessments were to made using visual analogue scales (VAS).

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
(b) (4)	(b) (4)	(b) (4)	3/24/05	6/10/05	VAI
(b) (4) (b) (4)	(b) (4)	(b) (4)	3/24/05	5/23/05	NAI

A. Protocol #DE013: "A Prospective, Multicenter, Randomized, Double-Blind, Active Comparator-Controlled, Parallel-Groups Study Comparing the Fully Human Monoclonal Anti-TNF Antibody Adalimumab Given Every Second Week with Methotrexate Given Weekly and the Combination of Adalimumab and Methotrexate Administered Over 2 Years in Patients with Early Rheumatoid Arthritis (PREMIER)"

1. Site: (b) (4). The data were acceptable.

   a. Twenty-eight subjects were enrolled at (b) (4) site. Ten records were reviewed in depth for the inspection.

   b. There were no limitations to the of inspection.

   c. Of the records reviewed 2 subjects were advanced to a higher dose of methotrexate more rapidly than the protocol permitted. Four subjects did not have various laboratory tests required by the protocol at recommended time intervals, and three subjects were not started on supplemental folic acid within the protocol guidelines. A Form FDA 483 was issued. (b) (4) responded in writing to the 483.

The changes he outlined seem adequate to correct the deficiencies and prevent their recurrence in future studies. It is unlikely that any of the deficiencies affected overall data integrity.

2. Site: [redacted] (b) (4) The data were acceptable.

   a. Sixteen subjects were enrolled at the site. Eight subject records were reviewed in depth for the inspection.

   b. There were no limitations to the inspection.

   c. The inspection did not disclose any significant deviations from federal regulations or from the study protocol. No Form FDA 483 was issued

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the studies appear to have been well conducted. The investigators, with some minor exceptions, adhered to the protocol. It is unlikely that any of the deficiencies had an adverse effect on data integrity or reliability.

No follow up action is indicated at either site other than routine, periodic surveillance.

{See appended electronic signature page}

Dianne Tesch
GCPB Reviewer
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Telecon

Teleconference Memorandum

Date:	08-03-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Erik Laughner
Re:	Adalimumab
STN:	125057.46

Discussion:

Jim Steck called to request a TCON with the Agency to review the revised labeling for the 125057_46 and 125057_58 supplements we provided.

125057/46

Laughner, Erik

From: Laughner, Erik
Sent: Monday, August 01, 2005 10:00 AM
To: 'James Steck'
Cc: Siegel, Jeffrey; Gorovets, Alex
Subject: Revisions to Abbott Label for Supplement 46 and 58

Importance: High

Hi Jim,

The Agency has reviewed the label to your efficacy and labeling supplement and attached are a "clean and red-line version" for your convenience.

If you have any questions or concerns, please feel free to give me a ring.

Sincerely,

Erik Laughner, M.S.
RPM
ODEVI/DRMP
301-594-6218.


HUMIRA CLEAN 080105 to Abbott...


HUMIRA CLEAN 080105 to Abbott....

Telecon

Teleconference Memorandum

Date:	07-25-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46 125057.58

Discussion:

Information request on the mean and median MTX dosage achieved in both groups and each group

Information request on the breakdown for the 3042 patients into the durations of exposure, i.e. how many patients were in the trials 1 year or longer, how many were 2 years or longer, 3 years or longer, 4, and 5.

125057_46

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: **July 6, 2005**

To: **Erik Laughner, M.S.**
Regulatory Project Manager
Office of Drug Evaluation VI
Division of Review Management Policy

From: **Catherine Gray, Pharm.D.**
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: **Draft Label Review**
Humira (Adalimumab) – 125057/46 and 125057/58 merged efficacy and safety supplement

Below is a summary of DDMAC's comments on the proposed labeling changes for Humira supplements 46 and 58. Please let us know if you have any comments or questions.

CLINICAL STUDIES
Lines 158-164

- Consider adding information on the Humira monotherapy portion of the study.
- Consider adding information on the MTX dosing regimen.

Line 170 – "TABLE 1: ACR Responses in Placebo Controlled Trials (Percent of Patients)"

- Studies I-IV are placebo controlled, but this table only presents results from Studies II and III. Consider renaming the table to "ACR Responses in Study II and Study III (Percent of Patients)."

Line 196: [redacted] (b) (4)

- This summary information is repetitive of information in the introductory section. DDMAC recommends deleting this information from this section of the PI.

Lines 197-199: "…combination treatment with HUMIRA plus MTX led to [redacted] (b) (4) and responses were sustained at Week 104."

- This presentation is promotional in tone. Is there substantial evidence to support this claim?
- This presentation suggests the same patients experienced the same ACR response at both week 52 and week 104. Were the data collected and evaluated on the same patients, or on

the dose groups? If the data were collected for the entire dose group, we recommend revising this presentation to reflect the nature of the data.
- Consider specifying which components of the ACR (20, 50 or 70) produced greater responses.

Lines 204-205: "Table 3: Clinical Responses in Study V (Percent of Patients)"
- Consider changing the title to "ACR Responses in Study V (Percent of Patients)" for consistency with Table 1.
- Consider rephrasing footnote a ("Major clinical response is achieving an ACR70 response for a continuous six month period") to the following: "Major clinical response is defined as achieving an ACR70 response for a continuous six month period."

Lines 208-209: "At Week 52, all individual components of the ACR response criteria for Study V improved in the HUMIRA/MTX group and improvements were maintained to Week 104."
- Were these improvements statistically significant for all of the components? Were the ACR components in the Humira/MTX treatment group greater than those observed in the MTX or Humira monotherapy groups?
- What about the results in the MTX or Humira monotherapy group? Including this information may provide helpful context to the reader.

Lines 226-227: (b) (4)
- This information seems inappropriate at this point in the label. Please consider moving it to the study introduction/description at the beginning of the Clinical Studies section.

Lines 227-231: " (b) (4)
- This presentation suggests that the same patients evaluated at week 52 had the same response ("maintained") at week 104. Was the study analysis performed on individual subjects, or were data collected on the group in a particular treatment regimen? Specifically, were the patients who comprised the N percent of responders at week 52 the same patients who comprised the N percent of responders at week 104? If the data analyzed the group of patients, we recommend revising this presentation to reflect the nature of this result.
- Was structural joint damage at 52 and 104 weeks compared to baseline values within groups or across groups?
- Recommendation for stylistic revisions to the paragraph: "Structural joint damage was assessed radiographically at Week 52 and Week 104 as the change in TSS and its components. The Week 52 results are shown in Table 5. Statistically significant differences for a change in TSS, erosion score and JSN were observed and maintained between HUMIRA plus MTX combination therapy and MTX monotherapy versus baseline."

Line 233: Table 5
- Consider presenting results from both Week 52 and Week 104.

Line 252: "... (b) (4) "

- This background information is repetitive. Please consider deleting this phrase from this section of the PI.

Line 253-255: "... (b) (4)

- Does this p-value apply to both components of the QOL measured for the Humira/MTX combination therapy versus MTX monotherapy?
- How often was the HAQ-DI and SF-36 measured during the second year of the study? If it was only assessed at Week 104, this claim of "maintained" is inappropriate.
- As mentioned earlier in this consult, if the data were analyzed by treatment group, we recommend revising the presentation to reflect this distinction. As currently presented, the claims suggest the same individuals maintained their same level of response at Week 104.
- Please consider adding information on the HAQ-DI and SF-36 results for the HUMIRA monotherapy group.

INDICATIONS AND USAGE

Line 258-259: "HUMIRA is indicated for reducing signs and symptoms, **including major clinical response**..." (emphasis added)

- Is there substantial evidence to support this claim?
- Not all competitors include this statement in the indication.

Line 261 (b) (4)

- Competitor labels did not add this statement to the Indications and Usage section when the indication was expanded to include patients with rheumatoid arthritis for less than 3 years. DDMAC recommends deleting this statement from the indication.

ADVERSE REACTIONS – Infections

Lines 523-524

- DDMAC suggests the following stylistic change: "These studies include reports of military, lymphatic, and peritoneal, as well as pulmonary, tuberculosis."

Lines 511-533

- This section discusses the scope and severity of infections reported following Humira therapy. However, the section does not include the fact that some of these infections (both opportunistic and tuberculosis) were fatal. DDMAC recommends adding this important risk information to this section of the label.

Telecon

Teleconference Memorandum

Date:	06-14-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Erik Laughner
Re:	Adalimumab
STN:	125057.46

Discussion:

To facilitate review of the draft labeling for both the 125057_46 and 125057_58 supplements simultaneously, the Agency requested a merged version of the changes from the Sponsor. This merged version should be submitted formally to both supplements.

Telecon

Teleconference Memorandum

Date:	06-14-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46 125057.58

Discussion:

1. In reference to malignancies:

- FDA requested information in a tabular form for all subjects in the controlled portions of the controlled trials that compare the number of malignancies per 100 patient-years in the Adalimumab containing arms to the number in arms without Adalimumab
- Break down the malignancies into the types (10 most frequent, excluding Lymphomas, and non-Melanoma skin cancers)
- Please provide us with he most recent European label for Adalimumab
- Please provide the timeline for the submission of this information
- Sponsor will submit this to the Safety Labeling Supplement
- Sponsor will submit information on Lymphomas and Non-Melanoma skin cancers in addition to the rest of the malignancies
- The sponsor will submit the information from the RA trials first, then the rest of it

2. In reference to the laboratory abnormalities in Adalimumab containing groups:

Please provide clarification and analysis of the previously submitted information on the following:

- Hypercalcemia, 4 cases in adalimumab monotherapy group
- Hyperglycemia, 25 grade 3 in 'mono", 13 grade 3 in "combo", 2 grade 4 in "combo"
- Hyperkalemia, 2 cases of grade 4 in "mono"

- Hyperurecemia, 31(!) of grade 4 in "mono"

3. In reference to the LFT abnormalities observed during the trial:

Brief narratives of grade 3 "over 52 weeks" and "discontinuations" to explore how soon they developed after the start of therapy; how high and how fast they became abnormal; whether there was any clinical liver disease or elevated bilirubin in any of these; how long the abnormalities continued and how high they got before the drug discontinuation; whether there were other factors contributing to he discontinuation; what other hepatotoxic drugs were involved; and whether there were any changes noted in the autoimmune markers that were coincidental with the LFT abnormalities

4. In reference to the Postmarketing report on the Hepatic Adverse Events:

Follow-up information on the cases involving ALT > 150, and one case with ALT > 500, cases still ongoing after the drug discontinuation.

06/01/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: Erik S. Laughner

Subject: Mid-Cycle Meeting

STN: 125057/46

Sponsor: Abbott

Product: adalimumab (Humira)

Indication: Treatment of rheumatoid arthritis

Date, Location, & Time of Meeting: May 31, 2005
WOC-2, 6th FL G
3:00 – 5:00 p.m.

FDA Representatives:

Alex Gorovets
Jeff Siegel
Ellis Unger
Boguang Zhen
Kurt Brorson
Dianne Tesch
Aloka Chakravarty
Erik Laughner
James Reese
Hsien Ju
Kyung Lee

Purpose:

To discuss outstanding issues regarding the review of Abbott's efficacy supplement and to present the status of the individual review disciplines.

Summary:

Major milestones were noted for this application and the upcoming first labeling meeting in early July. It was also brought to the attention of the review team that another labeling supplement 125057/58 for Abbott will be reviewed at the same time as the labeling meeting. This supplement is to revise the Precautions, Adverse Reactions, Warnings, and Patient Information sections of the package insert.

Summary of Review Status:

Clinical

- Safety and efficacy data was presented by Dr. Gorovets. The study is well designed and appears to have met its objective of expanding the indication. Adalimumab appears to be safe and well tolerated in subjects with early RA treated for 2 years.

- No recent amendments to this supplement have been classified as "major" amendments to date.

BiMo

- Inspections of (b) (4) and (b) (4) are in essence completed.

- Minor protocol deviations and some poor record keeping have been noted with (b) (4) (b) (4), but there is no evidence of intentional manipulation of data. This site most likely will be VAI.

Telecon

Teleconference Memorandum

Date:	05-25-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

1. FDA requested information on the number of subjects with only one film set and on the number of subjects with no film sets in each treatment group.

2. FDA requested a table with the number (%) of subjects in each group who had grade 2, 3, or 4 Adverse Events in Chemistry or Hematology over 52 weeks of the study (not at 52 weeks).

3. Please provide, for any laboratory category that is more frequent in any of the adalimumab groups, a breakdown by grade 2, 3, and 4.

4. Please provide the analyses of the lab-data requested above.

Telecon

Teleconference Memorandum

Date:	05-17-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

FDA requested LOCF method of imputation to be applied to the following major and "other" secondary endpoints, with the imputed numbers being specified for each treatment group and time-point (52 or 104 weeks):

- Change in SF36 Physical Components / week 52 / major / 2 groups
- Change in SF36 Mental Components / week 52 / major / 2 groups
- Change in ACR-N / week 52 + week104 / "other" / 3 groups
- Change in HAQ-DI / week 52 + week 104 / "other" / 3 groups
- Change in SF36 (Physical) /week 52 + week 104/"other"/3 groups

Li, Jianming

From: Hoyt, Colleen
Sent: Monday, May 16, 2005 12:40 PM
To: Li, Jianming
Subject: RE: Request for compliance check on Abbott Laboratories (STN 125057/45 and 125057/46)

A compliance review of the firms listed below has shown that all firms have had an acceptable inspection by Team Biologics within the last two years. There are no compliance actions that would prevent approval of STN 125057/45 and 125057/46 at this time.

Colleen

-----Original Message-----
From: Li, Jianming
Sent: Monday, May 09, 2005 1:37 PM
To: Hoyt, Colleen
Cc: Dietrick, John M; Rivera Martinez, Edwin; Smedley, Michael
Subject: Request for compliance check on Abbott Laboratories (STN 125057/45 and 125057/46)

Colleen,

Please conduct a compliance check on Abbott Laboratories facilities for the manufacturing of Adalimumab. The STN number is 1025057/45 and 125057/46, two Pre-Approval supplements. I plan to finish the reviews in two weeks. After that I will take a two-week vacation and then a two-week training a few days after the vacation. I will appreciate very much if you can have the compliance check done by 5/18.

The manufacturing sites are:

1. Abbott Laboratories, 200 Abbott Park Rd, Abbott Park, IL 60064. FEI: 1415939. Labeling and packaging, release of drug product,

2. Abbott Bioresearch Center, 100 Research Drive, Worcester, MA 01605, FEI: 3003684386, Manufacture, release, stability of drug substance.

3. [redacted] (b) (4), Formulation, filling and sterility testing, labeling and packaging o f vials and prefilled-syringes.

4. [redacted] (b) (4), Formulation and filling of vials.

5. Abbott GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany FEI: 3002807401. Release testing, stability testing, testing of excipients, release.

6. [redacted] (b) (4). Sterility testing of vial and pre-filled syringes.

Regards

Jim

Telecon

Teleconference Memorandum

Date:	05-10-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

FDA requested the following information in reference to the ACR components At week 52 and week 104:

- LOCF method of imputation instead of "as observed"
- Median instead of mean values, i.e. Baseline and median % change for each parameter

Telecon

Teleconference Memorandum

Date:	05-04-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

In response to the FDA request for the narratives of the 3 cases of patients who developed TB while on study treatment, Abbott informed us that they will be included with the rest of the TB-related information. It will be faxed, and then submitted as an amendment.

Telecon log

Teleconference Memorandum

Date:	04-21-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

Information was requested on 04-19-05 in reference to baseline CRP values at different sites.

The sponsor replied that for baseline CRP, 783 of the 799 subjects had their CRP values at Baseline performed by the central lab. The central lab used a normal range for CRP of 0 - 0.5 mg/dL. CRP values for the remaining 16 subjects were performed by one of seven other labs.

Telecon

Teleconference Memorandum

Date:	04-19-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

FDA requested the following information in reference to the cases of TB:

1. How were the patients being screened?
   How many with CXR alone?
   How many with PPD?
   How many with both?

2. How many patients who screened positive ended up being treated for TB and started on study treatment?

3. How long were they treated before Adalimumab was started?

4. US vs. non-US

5. In the non-US patients, what cut-off was used for a positive PPD?

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: March 28, 2005

To: Administrative File, **STN** 125057/46/3

From: Jianming Li, Facility Reviewer, CDER/OC/DMPQ/TFRB, HFD-328 JL 3/28/05
Carolyn Renshaw, Peer Reviewer, CDER/OC/DMPQ/TFRB, HFD-328 cmr 3/28/05

Through: Michael D. Smedley, Branch Chief, CDER/OC/DMPQ/TFRB, HFD-328 MDS 4/5/05

Subject: **Pre-Approval Supplement (PAS):** Revise labeling to include recently diagnosed patients with moderately to severe RA who have not received methotrxate.

Review of the applicant's claim for (b) (4)

Applicant: Abbott Laboratories

Product: Adalimumab

Indication: Improving physical function, reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active arthritis who had an inadequate response to one or more DMARDs.

Due Date: October 20, 2005

Recommendation: Information related to categorical exclusion have been reviewed and the submission is recommended for approval.

Review Narrative:
This PAS seeks to revise labeling to include recently diagnosed patients with moderately to severe RA who have not received methotrxate..

The scope of this TFRB review is limited to (b) (4). No other facility information

was included in the CMC section.

I. (b) (4)
The firm claimed (b) (4)

II. cGMP Status
A Compliance Check was completed by the Investigations and Preapproval Compliance Branch on May 16, 2005. A compliance review of the firms listed below has shown that all firms have had an acceptable inspection by Team Biologics within the last two years. There are no compliance actions that would prevent approval of STN 125057/46 at this time.

1. Abbott Laboratories, 200 Abbott Park Rd, Abbott Park, IL 60064. FEI: 1415939. Labeling and packaging, release of drug product,
2. Abbott Bioresearch Center, 100 Research Drive, Worcester, MA 01605, FEI: 3003684386, Manufacture, release, stability of drug substance.
3. (b) (4), (b) (4)), Formulation, filling and sterility testing, labeling and packaging o f vials and prefilled-syringes.
4. (b) (4), (b) (4)), Formulation and filling of vials.
5. Abbott GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany FEI: 3002807401. Release testing, stability testing, testing of excipients, release.
6. (b) (4), Sterility testing of vial and pre-filled syringes.

CC:
HFD-328: Renshaw
HFD-328: Smedley
HFD-320: Famulare
HFD-109: Laughner
HFD-328: TFRB Blue Files (STN 125057)

Date prepared: Li, 3/28/05
Comments by: Renshaw, 3/28/05

Archived File: S:\archive\BLAs|\125057\125057.46.3.ctg.exc.03-28-05.doc

Telecon log

Teleconference Memorandum

Date:	03-31-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:

Response to the information requested on 03-04-05 was communicated by telephone, (submitted as an amendment):

1. How many subjects terminated study treatment in each treatment arm but remained in the study?

Response: There were no subjects in the study who terminated treatment but remained in the study.

2. In each treatment arm, how many subjects were randomized but did not receive at least one dose of study drug?

Response: There were no subjects in the study who were randomized but did not receive at least one dose of study drug

3. How many subjects had only baseline X-ray films in the three treatment groups?

Response: There were 13 subjects in the methotrexate arm, 16 in the adalimumab arm and 9 in the combination group who only had baseline X-rays.

telecon

Teleconference Memorandum

Date:	03-04-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Alexander Gorovets, M.D.
Re:	Adalimumab
STN:	125057.46

Discussion:
FDA requested the following information:

1. How many subjects terminated study treatment in each treatment arm but remained in the study?

2. In each treatment arm, how many subjects were randomized but did not receive at least one dose of study drug?

3. How many subjects had only baseline X-ray films in the three treatment groups?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125057/46

FEB 18 2005

Abbott Laboratories
Attention: James D. Steck, R.Ph.
Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL, 60064-6157

Dear Mr. Steck:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated December 17, 2004, for Adalimumab to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your supplement today. The user fee goal date is October 20, 2005. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your supplement. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder biologics/default.htm for important information regarding therapeutic biological products, including the address for submissions Effective Oct 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Erik S. Laughner, M.S., at (301) 827-4358.

Sincerely,

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Filing Notification (FL) &

No Deficiencies Identified (NDI)

SS Data Check:
- **Communication**
- **Milestone: Confirm Filing Action Entry & Close Date**
- **If applicable – Confirm Deficiencies Identified Entry & Close Date**

USE IF FILING OR FILING WITH NO DEFICIENCIES IDENTIFIED

cc: Erik Laughner, HFD-109
Alex Gorovets, HFD-108
DRMP BLA file (hard copy)

History:
E. Laughner: 02/14/05; 02/17/05

File Name:
(S:\Laughner\BLA\125057\125057 46\125057 46 FL.doc)

Office	Name/Signature	Date
DRMP		021705
DRMP	Schneider	2-17-05
DRMS		2-17-05
DCMP	Kellie Townsend	2/18/05

BLA/NDA/PMA
Review Committee Assignment Memorandum

☐ Initial Assignment
☒ Change

STN: 125057/46

Applicant: Abbott Labs.

Product: adilmumab (Humira)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
		Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
	DDMAC	Labeling		
	Reviewer	Other		
Jianming (Jim) Lee	DMPQ	Facility	Mike Smedley	2/17/05

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Kurt Brorson	Reviewer	Safety Evaluator	Erik Laughner	02/17/05
Anita O'Connor	Reviewer	Pharm/tox	Erik Laughner	02/17/05

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Erik Laughner — Name Printed

Signature

02/17/05 — Date

Memo entered in RMS by: Kat Date: 2/22/05 QC by: LB Date: 2/25/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 31, 2005

From: *Erik S. Laughner, DRMP, HFD-108* ESL 01/31/05

To: STN 125057/46

Subject: Meeting Summary

Meeting Date: January 31, 2005 **Time:** 9:00 – 10:00 A.M.

Meeting Requestor/Sponsor: Internal

Product: adalimumab (Humira)

Proposed Use: To extend the current label to include recently diagnosed patients with moderately to severely active RA who have not been previously treated with methotrexate.

Type of meeting: Internal

Meeting Purpose: To determine whether STN may be filed.

DISCUSSION:

Clinical

Content and format of the electronic submission were suitable for filing. The X-ray content submission is suitable to the radiology reviewer.

This appears to be a well designed study and there does not appear to be any safety issues. The number of patients and the size of the safety database should be adequate.

There is no need for an advisory committee.

The BiMo reviewer will arrange the inspection assignments with input form the clinical reviewer.

One concern was the need to clarify the link of individual investigators with the clinical sites. Also to clearly link the number of patients at each site. Abbott was informed of this and will be providing an amendment.

A second issue to evaluate is the warning label concerning possible risk of lymphomas with product use. The apparent incidence of lymphoma now in the placebo group may indicate that this previous warning may be inappropriate.

A third issue was Abbott's request for [redacted] (b) (4)

All of the reviewers agreed that the supplement should be filed.

FDA Attendees:

Erik Laughner
James Reese
Alex Gorovets
Jeff Siegel
Catherine Gray
Bo Zhen
Lydia Martynec
Dianne Tesch
Kyung Lee
Ellis Unger

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125057/46 Product: Adalimumab Applicant: Abbott Labs

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date 01/31/05 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ✓ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Gavvets Kyung Lee _____ _____
- ☐ Memo of Filing Meeting

STN 125039/46 Product Adalimumab

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?		If not, justification, action & status
Cover Letter	Y	N	
Form 356h completed	Y	N	
▫ including list of all establishment sites and their registration numbers	Y	N	
▫ If foreign applicant, US Agent signature.	Y	N	N/A
Comprehensive Table of Contents	Y	N	
Debarment Certification with correct wording (see * below)	Y	N	
User Fee Cover Sheet	Y	N	
User Fee payment received	Y	N	
Financial certification &/or disclosure information	Y	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y	N	
Pediatric rule: study, waiver, or deferral	Y	N	(b) (4)
Labeling:	Y	N	
▫ PI –non-annotated	Y	N	
▫ PI –annotated	Y	N	
▫ PI (electronic)	Y	N	
▫ Medication Guide	Y	N	
▫ Patient Insert	Y	N	
▫ package and container	Y	N	
▫ diluent	Y	N	
▫ other components	Y	N	
▫ established name (e.g. USAN)	Y	N	
▫ proprietary name (for review)	Y	N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?		If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	N	
▫ legible	Y	N	
▫ English (or translated into English)	Y	N	
▫ compatible file formats	Y	N	
▫ navigable hyper-links	Y	N	
▫ interpretable data tabulations (line listings) & graphical displays	Y	N	
▫ summary reports reference the location of individual data and records	Y	N	

STN 125057/46 Product Adalimumab

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y (N)	
if CMC supplement:		N/A
☐ description and results of studies performed to evaluate the change	Y N	
☐ relevant validation protocols	Y N	
☐ list of relevant SOPs	Y N	
if clinical supplement:		
☐ changes in labeling clearly highlighted	(Y) N	
☐ data to support all label changes	(Y) N	
☐ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
☐ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? No

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one): File RTF

RPM Signature: Evik Laughner Branch Chief concurrence:

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Clinical overview [2.5]	(Y)	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
▫ Biopharmaceutics and associated analytical methods	(Y)	N	
▫ Clinical pharmacology [includes immunogenicity]	(Y)	N	
▫ Clinical Efficacy [for each indication]	(Y)	N	
▫ Clinical Safety	(Y)	N	
▫ Synopses of individual studies	(Y)	N	

CTD Module 5 Contents	Present?		If not, justification, action & status
Module Table of Contents [5.1]	(Y)	N	
Tabular Listing of all clinical studies [5.2]	(Y)	N	
Study Reports and related information [5.3]	Y	N	
▫ Biopharmaceutic	Y	(N)	Not applicable
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	(N)	"
▫ Pharmacokinetics (PK)	Y	(N)	"
▫ Pharmacodynamic (PD)	Y	(N)	"
▫ Efficacy and Safety	(Y)	N	
▫ Postmarketing experience	Y	(N)	"
▫ Case report forms	(Y)	N	
▫ Individual patient listings (indexed by study)	(Y)	N	
o electronic datasets (e.g. SAS)	(Y)	N	
Literature references and copies [5.4]	(Y)	N	

CDER Implementation Issues	Yes?		If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y)	N	
▫ legible	(Y)	N	
▫ English (or certified translation into English)	(Y)	N	
▫ compatible file formats	(Y)	N	
▫ navigable hyper-links	(Y)	N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y)	N	

Examples of Filing Issues	Yes?	Filing Decision Details
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y (N)	Not applicable
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes		Comments/Actions Taken
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	(N)	Not applicable
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	(N)	"
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Labeling adequately described?		Statistical analyses adequately described?			Case report tabulations adequately described?		Case report forms adequately described?		
BLA (b) (4)	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): (File) RTF

Reviewer: Kyung Yul Lee 1/31/05 Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

~~Branch Chief~~ Team Leader: Boris Gershon 1/31/05 Division. Director: Alaka Chakravarty 1/31/05
(signature/ date) (signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
▫ Biopharmaceutics and associated analytical methods	Y (N)	this supplement does not contain data relevant to these modules (N/A)
▫ Clinical pharmacology [includes immunogenicity]	Y (N)	
▫ Clinical Efficacy [for each indication]	(Y) N	
▫ Clinical Safety	(Y) N	
▫ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
▫ Biopharmaceutic	Y (N)	N/A
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y (N)	
▫ Pharmacokinetics (PK)	Y (N)	
▫ Pharmacodynamic (PD)	Y (N)	
▫ Efficacy and Safety	(Y) N	
▫ Postmarketing experience	(Y) N	
▫ Case report forms	(Y) N	
▫ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
▫ legible	(Y) N	
▫ English (or certified translation into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	(Y) N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes/No	Date of action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y (N)	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y (N)	N/A (safety analysis completed recently)

STN 125057/46 Product Humira

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y (N)	N/A
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	N/A
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study reports submitted?	Financial disclosure or certification submitted?	SAS & other electronic datasets complete & usable	BiMo sites identified
DE013	(Y) N	(Y) N NR	(Y) N	(Y) N NR pending
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

yes

Is an Advisory Committee needed?

no

Recommendation (circle one): (File) RTF

Reviewer: [signature] Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date) 1-24-05

Concurrence:

Branch Chief: [signature] Division. Director: [signature] 1/28/05
(signature/ date) 1/28/05 (signature/ date)

telecon

Teleconference Memorandum

Date:	01-13-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Erik Laughner
Re:	Adalimumab
STN:	125057.46

Discussion:

Told Sponsor that the Agency agreed to their request of a 120 day safety update wavier. However, the Sponsor was asked to provide a listing of all SAEs and detailed desciptions of any which suggest a new safety concern.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JAN 07 2005

Abbott Laboratories
Attention: James Steck, R.Ph.
Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Steck:

SUBMISSION TRACKING NUMBER (STN) BL 125057/46 has been assigned to your recent supplement to your biologics license application for Adalimumab received on December 20, 2004, to include recently diagnosed patients with moderately to severe rheumatoid arthritis who have not received Methotrexate.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner, at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: January 5, 2005

From: Erik S. Laughner, M.S.

STN: 125057/46

The following was relayed to the review team via e-mail. This serves as the First Committee meeting:

Abbott has submitted STN 125057/46 (adalimumab, Humira) to revise labeling to include recently diagnosed patients with moderately to severe RA who have not received Methotrexate. This efficacy supplement has a **10** month review clock.

This Supplement is availabe in electronic format. Please see the link below:

<<<\\CBS5042329\M\EDR Submissions\2004BLA\DCC60000436\BLA125057\Compound\ABT-Humira\Humira_sBLA-DE013\roadmap.pdf>>>

The review team is as follows:

Alex Gorovots, Chairperson (Clinical)
Erik Laughner, RPM
Kurt Brorson, Product
Kyung Lee, Stats
Anita O'Connor, Pharm/Tox
Dianna Tesch, DSI
Catherine Gray, DDMAC
Lydia Martynec, Clinical/Medical Imaging

The milestones associated with this submission are as follows:

COMMITTEE ASSIGNMENT	January 3, 2005
FIRST COMMITTEE MEETING	January 10 2005
FILING MEETING	February 3, 2005
FILING ACTION	February 18, 2005
FIRST ACTION DUE	October 20, 2005

CONCURRENCE PAGE

Letter Type: LETTER: Acknowledgment Letter (ACK)
Summary Text: (PAS)

SS & RIS Data Check:

- **If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".**
- **Communication**

RIS Data Check:

- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

cc: HFD-109/Erik Laughner
HFD-108/Alex Gorovets
HFD-141/Ayoub Suliman
DRMP BLA file (hard copy)

History: K. Townsend: 1.5.2005

File Name: S:\STN 2005\125057.46.PAS.doc

Division	Name/Signature	Date
DRMP		01/07/05
DRMP	Schneider	1-7-05
DRMP		1-7-05
DRMP	Kelly Townsend	1/12/05

BLA/NDA/PMA
Review Committee Assignment Memorandum

☒ Initial Assignment
☐ Change

STN: 125057/46

Applicant: Abbott Labs.

Product: adilmumab (Humira)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Erik Laughner	Reg. Project Manager	Admin/Regulatory	Kay Schneider	12/22/04
	Reviewer	Admin/Regulatory		
		Product*		
	Reviewer	Product*		
	Reviewer	Product		
Alex Gorovets	Chairperson	Clinical	Jeff Siegel	12/22/04
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
Anita O'Connor	Reviewer	Pharm/Tox	Martin Green	12/27/04
Kyung Lee	Reviewer	Biostatistics	Boguang Zhen	12/23/04
Dianne Tesch	Reviewer	BiMo	Ni Khin	12/28/04
	Reviewer	Safety Evaluator		
Kurt Brorson	Reviewer	CMC, ~~Facility~~*	Steven Kozlowski	12/23/04
Catherine Gray	DDMAC	Labeling	Marci Kiester	12/28/04
Lydia Martynec	Reviewer	Other	Lydia Martynec	01/03/05

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types:** chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Erik Laughner — Name Printed

E. K. J — Signature

01/03/05 — Date

Memo entered in RMS by: KaA Date: 2/17/05 QC by: LB Date: 2/25/05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: December 27, 2004

FROM: Marc Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of sBLA application review status
Sponsor: Abbott
Product: adalimumab (HUMIRA)
Indication: To provide revised labeling to include recently diagnosed patients with moderately to severe RA who have not received methotrexate.

TO: sBLA file STN 125057/46

The review status of this file submitted as a BLA application is designated to be:

(Standard) Priority