CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
BLA 125057/16

Trade Name: Humira®

Generic Name: adalimumab

Sponsor: Abbott Laboratories

Approval Date: 07/30/2004

Indication: Request to supplement biologics license application for adalimumab to expand 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

JUL 30 2004

Our STN: BL 125057/16

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:

Your request to supplement your biologics license application for Adalimumab to 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 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 are deferring submission of your pediatric studies for ages four to seventeen years until March 31, 2006. We are also deferring the submission of your pediatric studies for ages zero to less than four years until March 31, 2007.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 601.70. These commitments are listed below.

1. To continue study DE038, "A Multi-center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Human Anti-TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Rheumatoid Arthritis" which is currently ongoing. The protocol was filed to BB-IND 7627 June 28, 2002, and the study was initiated on September 13, 2002. Enrollment will be completed by March 31, 2004, and study completion will occur by March 31, 2005. The final study report will be submitted by March 31, 2006. Please note that this revises the schedule for PMC #5 in our approval letter of December 31, 2002 letter.

2. To evaluate the feasibility of conducting a study in patients age zero to less than 4 years, and if appropriate, submit a pediatric study plan or request a waiver by March 31, 2007.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125057. Submit all study final reports to your BLA, STN BL 125057. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "Required Pediatric Study Commitments". In addition, please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10 point font.

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 Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an 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.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

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 - New/Expanded Indication
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: S. Kozlowski, HFM-555
M. Walton, HFM-576
P. Swann, HFM-555
DARP BLA file, HFM-585
K. Weiss, HFM-500
B. Conner, HFM-588
J. Siegel, HFM- 582
L. Liang, HFM-582
M. Kiester, DDMAC, HFD-42
Catherine Miller, HFD-[redacted] 42
Jeanne Best, HFD - 410
Hyon Kwon, HFD-430
L. Martynec, HFM- 573
Bo-Guang Zhen, HFM- 711
J. Lloyd Johnson, HFD- 46
Grace Carmouze, HFD-960
Terrie Crescenzi, HFD-960
B. Duvall-Miller, HFD-020
C. Lee, HFM-570
IPCB, HFD-322
HFD-240/B. Poole
HFD-013/D. Taub, (ORP/DIDP w/revised labeling)
HFD-O13/H. Brubaker, (ORP/DIDP w/revised labeling)
Mary Dempsey, OPSS, HFD-400
P. Guinn, OEP, HFD-006

APPEARS THIS WAY ON ORIGINAL

History: B. Conner 7.28.04:1.29.04: T. Pagan-Motta: 7.~~29~~30.04

File Name: (S:\Conner\BLA\Letters\125057_16

Office	Name/Signature	Date
DRMP	Beverly Conner	7/30/04
DRMP	Schneider	7-30-04
DRMP	for Dye	7-30-04
PTPDRMP		7/30/04
DRMP	Doreen A. Pagan Motta	8.3.04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

LABELING

(No. 3799)
NEW

HUMIRA®
(adalimumab)

Rx only
Tear at Perforation to Dispense Patient Information

WARNING

RISK OF INFECTIONS

Cases of tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) have been observed in patients receiving HUMIRA.

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.

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

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

The efficacy and safety of HUMIRA were assessed in four 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 and III) or as monotherapy (Study II) 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.

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 Placebo-Controlled Trials (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.

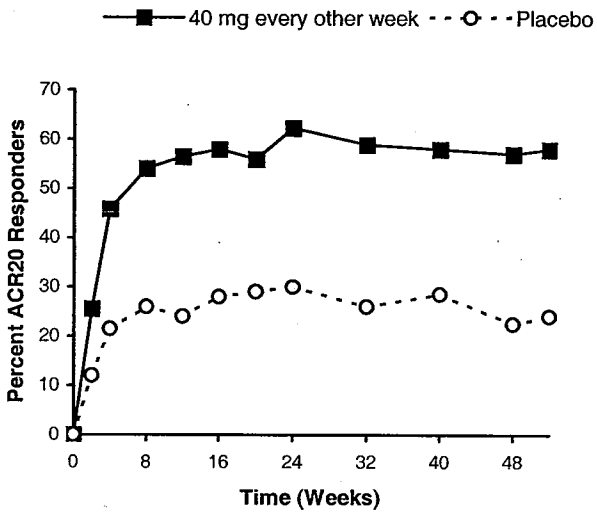
Table 2: Components of ACR Response in Studies II and III

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 52weeks. 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.

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

Table 3: 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.

Physical Function Response

In all four studies, 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.

INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

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

WARNINGS

SERIOUS INFECTIONS

SERIOUS INFECTIONS AND SEPSIS, 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. TUBERCULOSIS AND INVASIVE OPPORTUNISTIC FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF BLOCKING AGENTS INCLUDING HUMIRA.

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 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 all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active rheumatoid arthritis, 2 lymphomas were observed among 1380 HUMIRA-treated patients versus 0 among 690 control patients (mean duration of controlled treatment approximately 7 months). In the controlled and open-label portions of these clinical trials of HUMIRA in rheumatoid arthritis patients, 10 lymphomas were observed in 2468 patients over 4870 patient-years of therapy. This is approximately 5-fold higher than expected in the general population. 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. The potential role of TNF-blocking therapy in the development of malignancies is not known. (see **ADVERSE REACTIONS: Malignancies**).[4,5]

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 TNFα-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. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

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[6] 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 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**).

Thirteen cases of tuberculosis, including miliary, lymphatic, peritoneal, and pulmonary, were reported in clinical trials. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. Six cases of invasive opportunistic infections caused by histoplasma, aspergillus, and nocardia were also reported in clinical trials (see **WARNINGS**).

Malignancies

Among 2468 rheumatoid arthritis patients with moderately to severely active disease treated with HUMIRA in clinical trials for a mean of 24 months (4870 patient-years of therapy), 10 lymphomas were observed for a rate of 0.21 cases per 100 patient-years. This is approximately 5-fold higher than expected in an age- and sex-matched general population based on the Surveillance, Epidemiology, and End Results Database.[7] Rates in clinical trials for HUMIRA can not be compared to rates of clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. (see **WARNINGS: Malignancies**). An increased rate of lymphoma has been reported in the rheumatoid arthritis patient population. [5,6] Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma. The potential role of TNF-blocking therapy in the development of malignancies is not known. Thirty-eight malignancies, other than lymphoma, were observed. Of these, the most common malignancies were breast, colon, prostate, and uterine, which were similar in type and number to what would be expected in the general population.[7]

Autoantibodies

In the 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. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient 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 4 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 4: Adverse Events Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Rheumatoid Arthritis Studies

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

* Laboratory test abnormalities were reported as adverse events in European trials

** Does not include erythema and/or itching, hemorrhage, pain or swelling

Other Adverse Events

Other infrequent serious adverse events occurring at an incidence of less than 5% in patients treated with HUMIRA were:

Body As A Whole: Fever, infection, pain in extremity, pelvic pain, sepsis, surgery, thorax pain, tuberculosis reactivated

Cardiovascular System: Arrhythmia, atrial fibrillation, cardiovascular disorder, chest pain,

congestive heart failure, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, vascular disorder

Collagen Disorder: Lupus erythematosus syndrome

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

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**).

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 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. 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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NEWRevised: NEW

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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). RA is an inflammatory disease of the joints. People with RA are usually given other medicines for their disease before they are given HUMIRA. HUMIRA is for people with RA who have not responded well enough to these other medicines.

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 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.
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 the 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.

Before you start taking HUMIRA you should 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: If you develop a severe rash, swollen face or difficulty breathing while taking HUMIRA, call your doctor right away. 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 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.

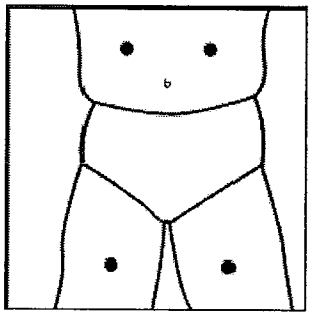
FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

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.

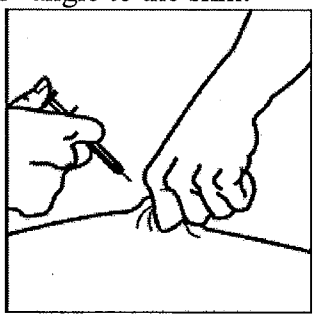
3) How to prepare your HUMIRA dose for injection with a Pre-filled Syringe

- 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.

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: NEW

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA supplement
Submission Number	STN 125057/16.0
Letter Date	July 30, 2004
Stamp Date	July 30, 2004
PDUFA Goal Date	July 30, 2004
Reviewer Name	Li-ching Liang, M.D. LCL CDER/ODE VI/DTBIMP
Through	Jeff Siegel, M.D. JS CDER/ODE VI/DTBIMP and Marc Walton, M.D., Ph.D. MW CDER/ODE VI/DTBIMP
Submission Date	Oct. 2, 2003
Review Completion Date	July 28, 2004
Established Name	Humira®
Therapeutic Class	TNF-Antagonist
Applicant	Abbott Labs
Priority Designation	S
Formulation	aqueous solution
Dosing Regimen	40 mg SQ QOW
Indication	Rheumatoid Arthritis
Intended Population	Moderately to Severely Active RA Patients

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommend approving the label supplement with revisions to the proposed label.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None are warranted at the present time.

1.2.2 Required Phase 4 Commitments

The Sponsor continues their commitment in providing periodic updates of the number of patients with malignancies (including lymphomas) and serious infections (including histoplasmosis and tuberculosis). No new Phase 4 commitments are required.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

The current submission provides 2-year clinical data from an open-label continuation study (Study DE019 OLE) involving rheumatoid arthritis (RA) patients on methotrexate (MTX) who were previously enrolled in a randomized, double-blind, placebo-controlled lead-in study (DE019). Two primary efficacy assessments were pre-specified by the Sponsor for Study DE019 OLE. The first efficacy endpoint, maintenance of improved physical function, would be demonstrated if 75% of Health Assessment Questionnaire Disability Index (HAQ DI) 0.5 unit Responder subjects at Week 52 of the original study maintained their responder status at the end of the open-label extension study (Week 104). The second efficacy endpoint, sustained inhibition of structural damage, would be demonstrated if $\geq$ 50% of subjects who had no change in their Total Sharp Score (TSS) at Week 52 also maintained that no change status at the end of the open-label extension study (Week 104).

The Sponsor met both primary efficacy endpoints, with consistent subgroup analyses and supportive secondary efficacy analyses that demonstrated clinical benefit for subjects continuing on long-term adalimumab treatment for active RA.

Direct comparison of adverse event (AE) rates between the first and second year of the study revealed no increase in overall AE rates or specific AEs attributable to continued adalimumab exposure. However, the development of malignancies and serious infections continues to be a concern in clinical trials with TNF-blockers. As such, the Sponsor continues to closely monitor these adverse events with periodic updates to the Agency.

1.3.1 Brief Overview of Clinical Program

Adalimumab was approved in the U.S. in December 2002 for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs. The current submission provides 2-year clinical data from Study DE019 and requests an extension of the indication for adalimumab for improvement in physical function.

1.3.2 Efficacy

The two pre-specified efficacy objectives were to determine whether adalimumab was able to (1) maintain improved physical function and (2) sustain inhibition of structural damage for subjects who received adalimumab in the lead-in Study DE019.

As such, subjects who achieved a ≥ 0.5 unit improvement in the HAQ DI score at Week 52 and were able to maintain that improvement to Week 104 were considered HAQ DI Responders. Using LOCF, 82% of all adalimumab-treated subjects achieved this endpoint. Using nonresponder imputation, 75% of all adalimumab-treated subjects achieved this endpoint.

Other clinical analyses, including the proportion of HAQ DI 0.22, 0.75, and 1.0 Responders, and the proportion of ACR20, ACR50, and ACR70 Responders, were consistent with this endpoint of subjects being able to maintain improved physical function. Subgroup analyses showed no significant differences in the level of HAQ DI response seen.

In support of the objective of sustained inhibition of radiographic progression, at Week 104, 54% of adalimumab-treated patients in Study DE019 had no increase in their TSS compared to Week 52. TSS data at Week 104 showed similar results in subjects previously randomized to adalimumab and those previously randomized to placebo in the lead-in study, indicative of the benefits of the open-label administration of adalimumab in Study DE019 OLE.

Secondary efficacy assessments, as well as quality of life assessments, were consistent with the two primary efficacy assessments.

1.3.3 Safety

The overall safety profile was comparable in the double-blind Study DE019 and the open-label extension Study DE019 OLE. The majority of reported AEs with adalimumab in this trial have been previously seen in other clinical trials and in the post-marketing use of TNF antagonists. The frequency of malignancies in Study DE019 OLE was similar to that seen in Study DE019, approximately 2% of subjects. Serious infectious AEs occurred in similar proportions of subjects (<4%) treated with adalimumab in both the double-blind and open-label periods.

1.3.4 Dosing Regimen and Administration

The open-label extension study used adalimumab 40 mg SQ QOW which is the currently approved dosing regimen.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were explored in this supplement.

1.3.6 Special Populations

The general RA population was studied; no special populations were identified.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Adalimumab is a human-derived monoclonal antibody to tumor necrosis factor-alpha (TNF-α) engineered by gene technology and does not contain non-human sequences. It binds only to TNF and has a half-life of approximately 2 weeks. This is in contrast to soluble TNF receptors (which bind both TNF and lymphotoxin with moderate to high affinity), and chimeric monoclonal antibodies (which bind only TNF but contain foreign protein sequences which are immunogenic). Clinical trial data with adalimumab, as well as the other two licensed TNF-blocking agents etanercept and infliximab, have demonstrated efficacy for improving signs and symptoms of RA as well as for inhibition of progression of structural damage. Adalimumab use is associated with several uncommon but serious adverse events, including serious infections and demyelinating disease. Lymphomas have been observed more frequently in RA patients receiving adalimumab than in the general US population. However, an increased risk of lymphomas has been observed in the RA patient population. Among adverse events occurring in at least 5% of treated patients, the only adverse events occurring ≥ 2% more frequently with

adalimumab than placebo were upper respiratory infection, sinusitis, abdominal pain, hypercholesterolemia, hyperlipidemia, increased alkaline phosphatase, headache, rash, accidental injury, injection site reaction, back pain, urinary tract infection, and hypertension.

2.2 Currently Available Treatments for Indication

Currently available treatments for the RA indication include non-steroidal anti-inflammatory drugs, corticosteroids, etanercept, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, anakinra, and infliximab.

2.3 Availability of Proposed Active Ingredient in the United States

This product is currently licensed and marketed in the United States. There are no known availability issues with the proposed ingredient.

2.4 Important Issues With Pharmacologically Related Products

An increased risk of serious infections and lymphoma is associated with currently approved TNF-antagonists.

2.5 Presubmission Regulatory Activity

N/A

2.6 Other Relevant Background Information

N/A

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There were no CMC changes proposed in this supplement.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology/toxicology data were submitted. The product is already approved and the dose used in this open-label study was the recommended dose and regimen in the label.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of clinical data for this review consisted of one Abbott-sponsored open-label clinical trial conducted in the United States and Canada at 83 study sites.

4.4 Data Quality and Integrity

The FDA did not inspect the clinical sites for this submission because there were deemed to be no grounds for inspection. The data presented in this review were from an open-label continuation study of a previously reviewed placebo-controlled study. The data were assessed to be complete. Of all randomized subjects, 75% completed the lead-in double-blind study (year 1) and 91% of subjects enrolling in the open-label study completed the study (year 2). Data sets were complete for enrolled subjects. The integrity of the data was assessed and deemed acceptable based on reproduction of the Sponsor's analyses by Agency biostatisticians and upon the internal consistency of the results.

4.6 Financial Disclosures

There were no financial disclosures indicating a potential for investigator bias. The study under review was an open-label continuation of a previously conducted double-blind, placebo-controlled study. The same investigators participated in the study under review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the INDICATIONS AND USE section, the Sponsor proposed the underlined text: "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."

6.1.1 Methods

The clinical data from the open-label study (DE019 OLE) were analyzed to support the proposed indication.

6.1.2 General Discussion of Endpoints

Two primary efficacy assessments were pre-specified in the statistical analysis plan for Study DE019 OLE:

1. **Maintenance of improved physical function for subjects originally receiving adalimumab in Study DE019.**

This was defined as the percentage of patients treated with adalimumab during Study DE019 who achieved a 0.5 unit or greater improvement in Week 52 HAQ DI ("HAQ DI 0.5 unit responder"), and then maintained an improvement of at least 0.5 u in HAQ DI at Week 104. Maintenance of improved physical function was demonstrated if 75% of HAQ DI 0.5 u responder subjects (with lower confidence limit $\geq$ 60%) at Week 52 maintained responder status at Week 104 (LOCF). The 75% value was pre-specified by the Sponsor in agreement with the Agency prior to the initiation of Study DE019 OLE. The choice of 75% of subjects maintaining a 0.5 u improvement in HAQ-DI as the cutoff for success was somewhat arbitrary but was chosen as a high bar for what is a subjective endpoint in an open-label trial. An improvement of 0.22 u in HAQ-DI has been demonstrated to be a clinically significant change. Therefore, an improvement of 0.5 u is a large change. Improvements of 0.5 u in HAQ-DI are uncommon in untreated patients. For example, in the lead-in study, 25% of placebo-treated subjects attained a HAQ-DI improvement of $\geq$ 0.5 u compared to 46% of adalimumab-treated subjects. Setting 75% of subjects maintaining improvement with a lower limit of the confidence interval of 60% as the cutoff would assure with confidence that a majority of subjects had maintained the improvement in physical function.

2. **Sustained inhibition of structural damage for subjects originally receiving adalimumab in Study DE019.**

This was defined as the change in structural damage (also called radiographic progression) evaluated by the change in Total Sharp Score (TSS) during the second year of treatment compared to Week 54. The Week 104 TSS change was defined as Week 104 TSS minus Week 52 TSS. The primary measure was the percentage of subjects with no change, defined as a change in the Total Sharp Score of less than or equal to zero during the second year of treatment with adalimumab. If $\geq$ 50% of subjects observed a difference of $\leq$ 0 units in the Week 104 TSS change (Week 104 TSS minus Week 52 TSS), or if the lower confidence limit of the observed percentage of subjects with no Week 104 TSS change was $\geq$ 37%, the two-year open-label TSS data would demonstrate sustained inhibition of radiographic structural damage. The 50% value was pre-specified by the Sponsor with the agreement of the Agency prior to the initiation of Study DE019 OLE. The choice of $\geq$ 50% of subjects observing a difference of 0 units in the week 104 TSS change compared to week 52 was somewhat arbitrary but was chosen to demonstrate that the improvements seen in the first 52 weeks of the trial were maintained with the second year of treatment given that no control arm was available for the second year. All patients were at risk of radiographic progression in this trial based on the inclusion criteria, even though all patients were receiving background methotrexate. In the lead-in study DE019 more

than half the placebo-treated patients (54%) had an increase in their erosion score (one component of the TSS) compared to fewer than half the adalimumab-treated patients (38%). Therefore, meeting a cutoff of $\geq$ 50% of subjects having no increase in TSS in the second year would support the hypothesis of continued inhibition of progression of structural damage.

6.1.3 Study Design

Study DE019 OLE was an open-label continuation study (conducted at 83 sites in the U.S. and Canada) involving RA subjects receiving MTX who were previously enrolled in **Study DE019**, a double-blind placebo-controlled lead-in study.

All subjects who completed Week 52 of lead-in Study DE019 were allowed to participate in this open-label continuation study, in which they all received open-label adalimumab 40 mg SC every other week (QOW), irrespective of their prior randomization assignment. The first subject entered Study DE019 OLE on March 01, 2001, and the last subject's final visit for this continuation study occurred on Sept. 18, 2002. This study was designed to assess the efficacy and safety of long-term adalimumab administration.

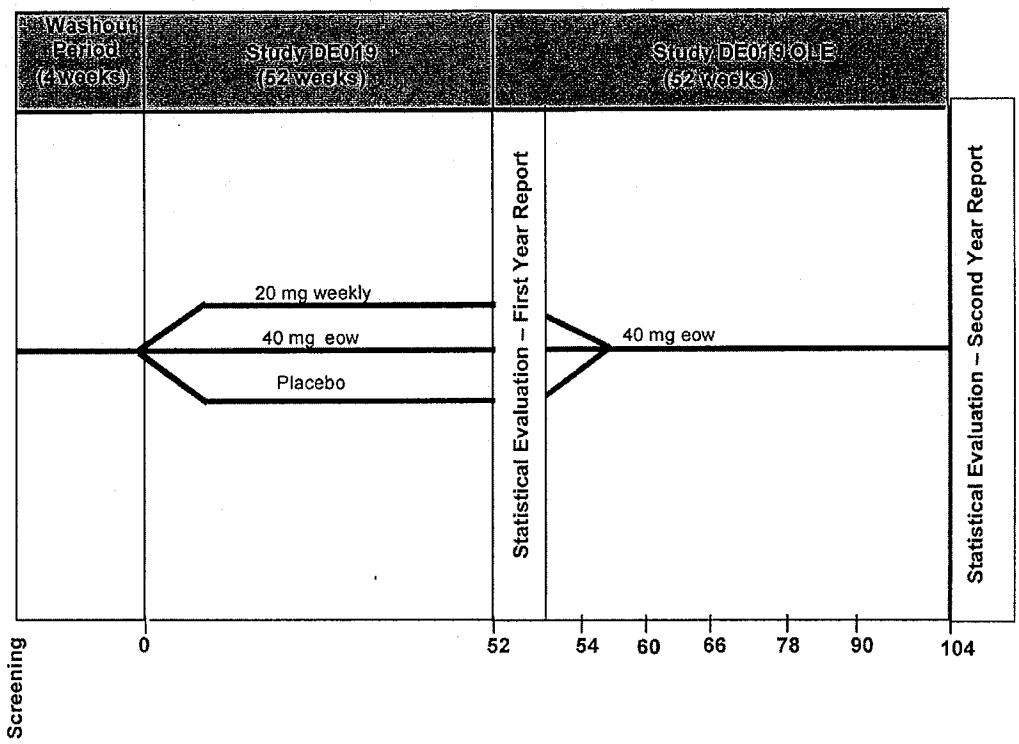
All patients in DE019 OLE self-administered adalimumab 40 mg sc QOW for a total of 2 years (including Study DE019) provided that they were suitable for entry based on inclusion and exclusion criteria. Blinded X-ray readers were used in Study DE019 OLE to ensure that joint status assessments were objective. The subjects' treatment randomization assignments in the blinded, lead-in study remained blinded until the Study DE019 database was locked.
The study design schematic for Studies DE019 and DE019 OLE is displayed in **Figure 1**.

The primary efficacy endpoints and statistical methods are discussed in section 6.1.2. In addition to the primary efficacy endpoints, the study protocol specified the following secondary endpoints:

Secondary Efficacy Parameters

Number of HAQ DI responders at 0.22, 0.50, 0.75, and 1.0 levels
Maintenance of Improved Physical Function (HAQ DI for 0.22, 0.75, and 1.0 responders)
Mean HAQ DI scores
Subgroup analysis for the HAQ DI
Total Sharp Score
Sustained Inhibition of Structural Damage as Measured by the 0.5 Level of the TSS
Subgroup analysis for Total Sharp Score
Total Erosions
No Erosion Score Change Between Week 52 and Week 104
Subgroup Analysis of Subjects with Change of Less Than or Equal to Zero in Erosion Score at Week 52 and Followed to Week 104
Joint space narrowing score
Yearly progression in Total Sharp Score
ACR20, ACR50, ACR70, and ACR100 responses
Major Clinical Response
SF-36 Questionnaire

Figure 1: Schematic of Studies DE019 and DE019 OLE



Entry Criteria:

The inclusion/exclusion study criteria in Study DE019 OLE were identical to those from the lead-in Study DE019, as only patients who completed the lead-in study were eligible to continue adalimumab during the open-label extension period.

Inclusion Criteria for Study DE019 OLE:

1. Met the ACR criteria for diagnosis of active RA and had at both the Screening and DE019 Week 0 Visits ≥ 6 swollen joints, ≥ 9 tender joints, and a C-reactive protein (CRP) ≥ 1 mg/dL, despite a minimum of 3 months of treatment with MTX. Distal interphalangeal joints were not included in joint counts for inclusion. The Screening and DE019 Week 0 Visits were 3 to 28 days apart for subjects who had not previously received DMARDs other than MTX, or 4 to 6 weeks for subjects who required a DMARD washout period. [Based on changes made in Amendment B, the CRP ≥ 1 mg/dL requirement was deleted from this criterion and incorporated into the sixth inclusion criterion bullet below.]

2. On a stable dose of MTX (oral, intramuscular, or sc) for at least 4 weeks prior to the Screening Visit.

3. Insufficient efficacy with MTX at doses of 12.5 to 25 mg. Subjects receiving 10 mg of MTX with documented intolerance to higher doses were also eligible for enrollment.

4. If a subject was on a second-line treatment (DMARD) other than MTX, they discontinued it for at least 28 days before the DE019 Week 0 Visit (washout period).

5. Treatment with oral folic acid 1-3 mg/day or, if appropriate, up to 10 mg leucovorin per week.

6. Rheumatoid factor (RF) positivity or at least one erosion on x-ray. *[Based on changes made in Amendment B, subjects were eligible if they had both RF positivity and a CRP ≥ 1 mg/dL, or at least one erosion on x-ray.]*

7. Subjects receiving daily glucocorticoids equivalent to ≤ 10 mg of prednisone or prednisone equivalent, were allowed into the study, but the dose could not be changed for at least 30 days. *[Amendment B clarified that the dose could not be changed for at least 30 days prior to enrollment.]*

8. Age 18 years and older.

9. Able and willing to self-administer sc injections or had available qualified person(s) to administer sc injections.

10. A negative pregnancy test (serum) for women of childbearing potential.

11. All male and female subjects of reproductive potential were required to use a reliable method of contraception.

12. Subjects were able and willing to give written informed consent and to comply with the requirements of the study protocol.

Exclusion Criteria for Study DE019 OLE

1. A history of or current acute inflammatory joint disease of different origin (*i.e.*, mixed connective tissue disease, seronegative spondyloarthropathy, psoriatic arthritis, Reiter's syndrome, systemic lupus erythematosus, or any arthritides with onset prior to age 16 years).

2. Prior exposure to alkylating agents such as chlorambucil or cyclophosphamide.

3. Wheelchair bound or bedridden subjects.

4. Pregnant or breast-feeding females.

5. Known positive human immunodeficiency virus (HIV) status.

6. A history of clinically significant drug or alcohol abuse in the last year.

7. History of intravenous (iv) drug abuse.

8. Positive serology for hepatitis B or C indicating infection as required for accepted standard of care for subjects receiving MTX.

9. History of active infection with listeria or tuberculosis.

10. Any ongoing chronic or active infection or any major episode of infection requiring hospitalization, treatment with iv antibiotics within 30 days, or oral antibiotics within 14 days prior to the Screening Visit.

11. Advanced or poorly treated diabetes with a documented history of recurrent infections.

12. Intra-articular, intramuscular, or iv administration of corticosteroids within 4 weeks prior to the Screening Visit.

13. Joint surgery in the joints assessed in this study within 2 months prior to the Screening Visit.

14. Treatment with any other investigational agent within 30 days or five half-lives of the agent prior to Screening evaluation.

15. Treatment with any investigational biologic agent, including anti-CD4 antibody, within 6 months prior to the Screening Visit.

16. Preceding treatment with any TNF antagonist, including adalimumab.

17. Unstable ischemic heart disease, active inflammatory bowel disease, active peptic ulcer disease, recent stroke (within 3 months), or poorly controlled medical condition.

18. History of lymphoma or leukemia.

19. History of any other malignancy within the past 5 years, with the exception of

successfully treated non-metastatic basal cell or squamous cell carcinomas of the skin and/or localized carcinoma *in situ* of the cervix.

20. Laboratory values that were suggestive of possible MTX toxicity, such as:

A. Male subjects with a hemoglobin value less than 9.0 g/dL (5.28 mmol/L) and female subjects with a hemoglobin value less than 8.5 g/dL (4.97 mmol/L).

B. Total white blood cell count (WBC) less than 3×10^9/L.

C. Platelet count less than 100×10^9/L.

D. Serum aspartate transaminase (AST) or alanine transaminase (ALT) values greater than twice the upper limit of normal range of the laboratory, or a total bilirubin value ≥3 mg/dL (≥ 51 μmol/L).

E. Serum creatinine values greater than 1.6 mg/dL for women or 1.8 mg/dL for men, or with proteinuria (4+ by dipstick or greater than 350 mg/24 hours).

Efficacy and Safety Measurements Assessed and Flow Chart

A summary of efficacy and safety parameters measures and the time points at which they were made during Study DE019 OLE is presented in **Table 1.**

Table 1: Schedule of Study Events (Study DE019 OLE)

		STUDY DE019 OLE							
Procedure	Week 52 (DE019)	Week 54	Week 60	Week 66	Week 78	Week 90	Week 104	Early Term.	Follow-Up[f]
RA & Non RA Concom. Meds	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Physical Examination	X						X	X	
ACR Parameters[a]	X	X	X	X	X	X	X	X	X
Morning Stiffness	X	X	X	X	X	X	X	X	
X-ray of Hands and Feet	X						X	X	
Disability Index of HAQ/VAS	X	X	X	X	X	X	X	X	
Short Form 36 Questionnaire	X			X	X	X	X	X	
Health Utilities Index	X				X		X	X	
FACIT Fatigue	X				X		X	X	
General Laboratory	X	X	X	X	X	X	X	X	
Pharmacokinetic Serum[b]	X				X	X	X	X	
Cytokines	X								
CRP	X	X	X	X	X	X	X	X	
RF	X						X	X	
Markers (serum)	X								
Human Anti-human Antibodies	X				X		X	X	X
Anti-nuclear Antibodies	X				X		X	X	
Anti-dsDNA[c]	X				X		X	X	
Adverse Events	X	X	X	X	X	X	X	X	X
Urinalysis (dipstick)[d]	X	X		X	X	X	X	X	
Study Drug Administration[e]		X	X	X	X	X	X		

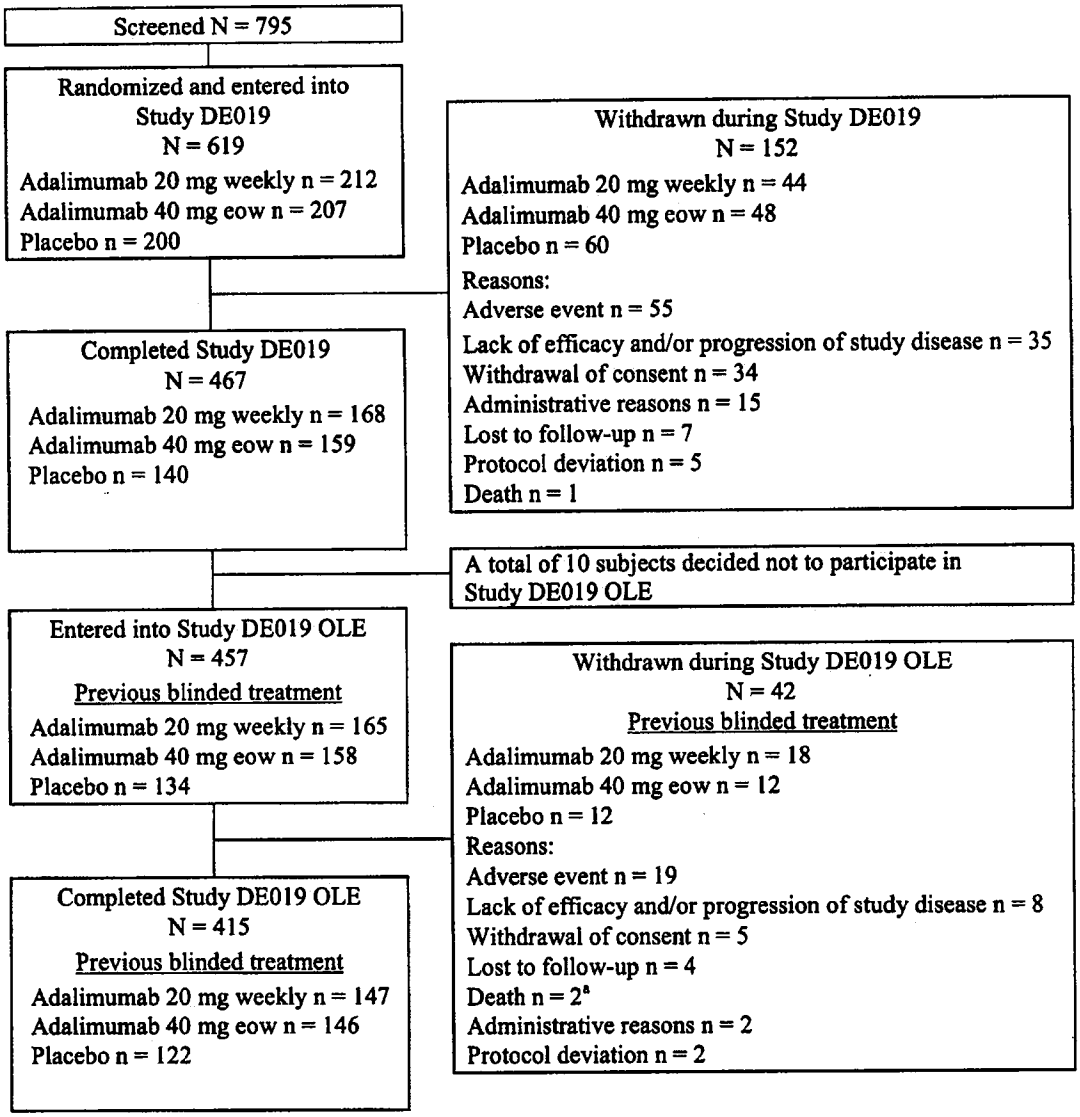
a ACR parameters include TJC and SJC, patient and physician global assessment of disease activity, and patient assessment of pain.
b PK samples were obtained prior to adalimumab administration at the respective visit.
c Performed automatically by central lab if ANA was elevated from DE019 baseline.
d Microscopic urinalysis was done only if dipstick was abnormal.
e Week 52 was the last assessment for Study DE019, no administration of drug occurred. Week 54 was the first administration of Study DE019 OLE treatment
f The follow-up visit was only for subjects who did not continue in Study DE019 OLE beyond Week 104.

6.1.4 Efficacy Findings

Subject Disposition

795 RA patients were screened for lead-in Study DE019, with 619 subjects eventually randomized into the study. 467 of 619 (75%) subjects completed the lead-in study and were allowed to participate in the open-label extension (OLE) study (**Figure 2**). Ten subjects decided not to participate in Study DE019 OLE, leaving 457 subjects who received open-label adalimumab 40 mg sc QOW.

Figure 2: Subject Disposition for Studies DE019 and DE019 OLE



a A third subject died 2 days after withdrawing due to an AE and is listed as being withdrawn due to that AE.

A total of 415 of 457 (91%) subjects completed Study DE019 OLE. 42 of 457 (9%) subjects prematurely withdrew from the study. Of these, 19 withdrew due to an AE (**Table 2**); 8 subjects withdrew due to lack of efficacy and/or progression of study disease; 5 subjects withdrew due to withdrawal of consent; 4 subjects were lost to follow up; 3 subjects died; 2 subjects withdrew due to administrative reasons; and 2 subjects withdrew due to protocol deviations.

Table 2: Summary of Subject Final Status (All Treated Subjects)

	Adalimumab 40 mg QOW (N=457) n (%)
Full Analysis Set	457 (100)
Completed 104 week study	415 (91)
Early Discontinuation	42 (9)
Discontinuations Due To:	
Adverse Event	19 (4)
Lost to Follow-Up	4 (1)
Protocol Violation	2 (<1)
Death	2 (<1)[a]
Withdrawal of Consent	5 (1)
Lack of Efficacy and/or Progression Of Study Disease	8 (2)
Administrative Reasons	2 (<1)

[a]an additional subject died, listed as due to an AE for a total of 3 deaths

Of the 19 of 457 (4%) subjects who discontinued the OLE study due to an adverse event, 14 had received adalimumab in the lead-in study, **Table 3.**

Table 3: Summary of Subject Final Status by Original Randomization Assignment (All Treated Subjects)

	20 mg QW (N=165) n (%)	**40 mg QOW (N=158) n (%)**	**Placebo (N=134) n (%)**
Full Analysis Set	165 (100)	158 (100)	134 (100)
Completed 104 Weeks' Study	147 (32)	146 (32)	122 (27)
Early Discontinuation	18 (11)	12 (8)	12 (9)
Discontinuations due to:			
Adverse Event	11 (7)	3 (2)	5 (4)
Lost to Follow-up	2 (1)	1 (<1)	1 (<1)
Protocol Violation	0 (0)	1 (<1)	1 (<1)
Death	1 (<1)	0 (0)	1 (<1)
Withdrawal of Consent	2 (1)	0 (0)	3 (2)
Lack of Efficacy and/or Progression of Study Disease	1 (<1)	6 (4)	1 (<1)
Administrative Reasons	1 (<1)	1 (<1)	0 (0)

Demographics

The demographic characteristics for all treated subjects in both studies DE019 (**Table 4**) and DE019 OLE (**Table 5**) are presented in this section.

Table 4: Demographic Characteristics, by Treatment Group, Lead-In Study DE019

	Adalimumab (D2E7)			
	20 mg wk **(N=165) n (%)**	***40 mg QOW*** **(N=158) n (%)**	**All Adalimumab (N=323) n (%)**	**Placebo (N=134) n (%)**
Age Group (yr)				
< 40	7 (4)	19 (12)	26 (8)	10 (8)
40-64	109 (66)	88 (56)	197 (61)	92 (69)
65-74	39 (24)	38 (24)	77 (24)	26 (19)
≥ 75	10 (6)	13 (8)	23 (7)	6 (5)
Gender				
Female	124 (75)	121 (77)	245 (76)	95 (71)
Male	41 (25)	37 (23)	78 (24)	39 (29)
Race				
Black	10 (6)	10 (6)	20 (6)	8 (6)
White	139 (84)	139 (88)	278 (86)	113 (83)
Hispanic	11 (7)	4 (3)	15 (5)	9 (7)
Asian	2 (1)	4 (3)	6 (2)	2 (2)
Other	3 (2)	1 (<1)	4 (1)	2 (2)
Weight Category (kg)				
≤ 60	28 (17)	33 (21)	61 (19)	18 (13)
> 60-70	29 (17)	33 (21)	62 (19)	33 (25)
>70-85	60 (36)	40 (25)	100 (31)	38 (28)
>85	48 (29)	52 (33)	100 (31)	45 (34)

Subjects who entered lead-in Study DE019 represented the typical rheumatoid arthritis population in clinical trials (**Table 4**). The majority of subjects were aged 40-64 years, female, and White. There were no major discrepancies between the demographics of adalimumab-treated subjects vs. placebo-treated subjects. 14% of the total study population were comprised of non-Whites.

Table 5 displays the demographic characteristics of patients randomized into Study DE019, those who received adalimumab treatment in Study DE019, and those who entered into extension Study DE019 OLE. Subjects in both Studies DE019 and DE019 OLE had comparable demographics.

Table 5: Demographic Characteristics for Patients Entering Study DE019 OLE

Demographic Characteristic	All treated subjects DE019 (N=619)	Entry into Study DE019 Subjects Previously Treated with Adalimumab (N = 323)[a]	Baseline (Week 0) Data for Subjects Entering Study DE019 OLE (N = 457)
Age (years)			
Median	57	58	58
Age group n (%)			
<40	55 (9)	26 (8)	36 (8)
40 - 64	402 (65)	197 (61)	289 (63)
65 - 74	130 (21)	77 (24)	103 (23)
≥ 75	32 (5)	23 (7)	29 (6)
Sex n (%)			
Female	464 (75)	245 (76)	340 (74)
Ethnic origin n (%)			
Caucasian	520 (84)	278 (86)	391 (86)
Black	39 (6)	20 (6)	28 (6)
Hispanic	42 (7)	15 (5)	24 (5)
Asian	9 (2)	6 (2)	8 (2)
Other	9 (2)	4 (1)	6 (1)
Body weight (kg)			
Median	76	76	76
Body weight category (kg)			
<60	110 (18)	61 (19)	79 (17)
> 60-70	124 (20)	62 (19)	95 (21)
> 70-85	187 (30)	100 (31)	138 (30)
> 85	197 (32)	100 (31)	145 (32)
Height (1cm)[b]			
Median	165	165	165

a Subjects who entered study DE019 OLE who were randomized to adalimumab during study DE019.

b One patient did not have a height recorded.

Concomitant Medications

The numbers of subjects on concomitant therapies during the OLE study are presented in **Table 6**. Nearly all subjects were on methotrexate (MTX) and folate. Approximately 50% of subjects were on concomitant steroids, and approximately ¼ of subjects were on acetaminophen and non-steroidal anti-inflammatory drugs.

Table 6: Number (%) of Subjects with Most Frequently (≥ 7%) Reported Concomitant Therapies During Study DE019 OLE, (All Treated Subjects)

Study DE019 OLE Concomitant Therapies[a,b] Preferred Term	(N = 457) n (%)
Methotrexate	452 (99)
Folic acid (folate sodium)	448 (98)
Prednisone (Deltasone)	222 (49)
Acetaminophen	127 (28)
Celebrex	120 (26)
Multivitamins	115 (25)
Calcium	114 (25)
Alendronate sodium	77 (17)
Estrogens conjugated	75 (16)
Rofecoxib	74 (16)
Acetylsalicylic acid	73 (16)
Vitamin E	69 (15)
Ascorbic acid	68 (15)
Acetaminophen with hydrocodone bitartrate	53 (12)
Advil	53 (12)
Darvocet-N	51 (11)
Fluzone	51 (11)
Levothyroxine	46 (10)
Losec	44 (10)
Lidocaine	43 (9)
Aleve	42 (9)
Azithromycin	42 (9)
Feosol	42 (9)
Lansoprazole	39 (9)
Aristocort	37 (8)
Depo-medrol	37 (8)
K-Dur	36 (8)
Amoxicillin	35 (8)
Atorvastatin	34 (7)
Hydrazide	33 (7)
Calcium with Vitamin D	32 (7)
Ranitidine	32 (7)

a Reported therapies were grouped to combine similar therapies that were listed under different names.
b Subjects may appear in more than one therapy class.

The route of administration, dose, and proportion of subjects on MTX were comparable for subjects entering the lead-in study and the open-label study (**Table 7**). Subjects in the open-label study were on a mean dose of 16mg MTX primarily via the oral route.

Table 7: Summary of MTX Administration at Baseline (All Treated Subjects)

	Baseline	
	Study DE019 (N=619)	**Study DE019 OLE (N=457)**
Route of Administration		
P.O.	418 (68)	313 (69)
Parenteral	202 (33)	128 (28)
MTX Dose		
N	619	441
Mean	17	16
Median	15	15

Baseline Disease Characteristics

The disease characteristics for the adalimumab-treated subjects in Study DE019 were also comparable to subjects enrolled in the OLE Study (**Table 8**). The disease characteristics of those enrolled in the OLE study were characteristic of RA patients with moderately to severely active disease.

Table 8: Disease Characteristics for Studies DE019 and DE019 OLE

Demographic Characteristic	Entry into Study DE019 Subjects Previously Treated with Adalimumab (N = 323)[a]	Baseline (Week 0) Data for Subjects Study DE019 OLE (N = 457)
Duration of RA (years)		
N	322	456
Median	8.4	8.2
Duration of Morning Stiffness (min)		
N	319	451
Median	60	60
TJC (0-68 joints)		
N	323	457
Median	25	26
SJC (0-66 joints)		
N	323	457
Median	18	17
Patient Assessment of Pain (100 mm VAS)		
N	323	457
Median	58	58
Patient Global Assessment of Disease Activity (100 mm VAS)		
N	323	457
Median	52	52
Physician Global Assessment of Disease Activity (100 mm VAS)		
N	323	457
Median	64	63
CRP (mg/dL)		
N	323	457
Median	1	1
HAQ DI		
N	323	456
Median	1.5	1.5

a Subjects who entered study DE019 OLE who were randomized to adalimumab during study DE019.

Maintenance of Improved Physical Function

The Preservation of HAQ DI for 0.50 unit Responders at Week 104

The percent of 0.22 unit HAQ DI and 0.50 unit HAQ DI responders at Week 52 from the original one year lead-in Study DE019 is presented in **Table 9** for reference. 46% of subjects randomized to receive adalimumab 40 mg QOW achieved a HAQ DI response of 0.5 units compared to 25% of subjects who received placebo. In this lead-in study, the LOCF method of analysis was used to impute missing data.

Table 9: Percent of HAQ DI Responders from Lead-in Study DE019

Level of HAQ DI Response In Study DE019	Dose Assignment in Study DE019	
	40 mg QOW	Placebo
0.22 HAQ DI Responders	60%	41%
0.50 HAQ DI Responders	46%	25%

After an additional year of adalimumab treatment, 82% (167 of 204) HAQ DI 0.50 responders, previously randomized to adalimumab treatment in Study DE019, remained HAQ DI 0.50 responders (95% CI, 77% - 87%) in the LOCF analysis, **Table 10.** This result met the pre-specified endpoint of having at least 75% of subjects who achieved a reduction in HAQ DI of 0.5 units at Week 52, maintained at least that improvement at Week 104, and had the lower limit of the CI above 60%. This result is consistent with a conclusion of maintenance of improved physical function following two years of treatment with adalimumab. The disadvantages of this open-label continuation study design are a lack of a control group and no strict intent-to-treat analysis. These results were verified by FDA biostatisticians.

Table 10: Maintenance of Improved Physical Function: Preservation of the HAQ DI for 0.50 unit Responders (Week 52 HAQ DI 0.50 unit Responder Subset Subjects)

	Treatment Assignment in Study DE019		
	20 mg weekly n (%)	**40 mg QOW n (%)**	**All Adalimumab n (%, 95% CI)**
0.50 HAQ DI responders at Week 52, n	109	95	204
0.50 responders at Week 104 (LOCF)	87 (80)	80 (84)	167 (**82**, 77 - 87)
0.50 responders at Week 104 (as observed)	76 (70)	76 (80)	152 (**75**, 69 - 81)

QOW: every other week, LOCF: last observation carried forward

To address the potential for bias in the Sponsor's pre-specified HAQ endpoint, the Agency performed an intention-to-treat analysis using a categorical endpoint of success or failure. **Table 11** and **Table 12** display the number of subjects who attained a $\geq$ 0.5 unit HAQ DI score at Weeks 52 and 104 according to their randomized dose in lead-in Study DE019 (as determined by the LOCF and non-responder imputation techniques, respectively). In both tables presented, the definition of a "Responder" was more stringent than for the Sponsor's analysis: "Week 52 Responders" were those subjects who attained a $\geq$ 0.5 unit improvement in HAQ DI score at both Weeks 24 and 52, whereas "Week 104 Responders" were subjects who had a $\geq$ 0.5 unit improvement in the HAQ DI score at Weeks 24, 52, 78, and 104, indicating a durable HAQ response.

Using the LOCF analysis (**Table 11**), 45% of all adalimumab-treated patients vs. 22% of placebo-treated patients were Week 52 Responders. 39% of adalimumab-treated patients vs. 21% of placebo-treated patients were Week 104 Responders.

Table 11: Number (%) Subjects with Improvement in HAQ DI of ≥ 0.5 unit – FDA Responder Analysis (LOCF)

		Randomized Dose in Study DE019		
Period	**Responder Status**	**20 mg weekly (N=212) n (%)**	**40 mg QOW (N=207) n (%)**	**Placebo (N=200) n (%)**
52 Weeks *	Responder	101 (48)	89 (43)	44 (22)
	Non-responder	111 (52)	118 (57)	156 (78)
104 Weeks **	Responder	85 (40)	77 (37)	42 (21)
	Non-responder	127 (60)	130 (63)	358 (79)

* A Responder at Week 52 had ≥ 0.5 unit improvement in HAQ DI score at **Weeks 24 and 52**

** A Responder at Week 104 had ≥ 0.5 unit improvement in HAQ DI score at **Weeks 24, 52, 78, and 104**

This nearly 2:1 response ratio between adalimumab-treated subjects vs. placebo-treated patients is similarly seen in **Table 12** when the non-responder imputation technique is used. It should be noted, however, that the "placebo-treated" group was not a true placebo subpopulation because placebo-treated patients in lead-in Study DE019 received open-label adalimumab 40 mg QOW from Weeks 52 to 104. Overall, the results of this intention-to-treat analysis support durable improvement in physical function out to 2 years.

Table 12: Number (%) Subjects with Improvement in HAQ DI of ≥ 0.5 unit – FDA Responder Analysis – Discontinued Patients Imputed as Non-Responders

		Randomized Dose in Study DE019		
Visit	**Responder Status**	**20 mg weekly (N=212) n (%)**	**40 mg QOW (N=207) n (%)**	**Placebo (N=200) n (%)**
Week 52 *	Responder	87 (41)	73 (35)	35 (18)
	Non-responder	125 (59)	134 (65)	165 (83)
Week 104 **	Responder	58 (27)	57 (28)	31 (16)
	Non-responder	154 (73)	150 (73)	169 (85)

* A Responder at Week 52 had ≥ 0.5 unit improvement in HAQ DI score at **Weeks 24 and 52**

** A Responder at Week 104 had ≥ 0.5 unit improvement in HAQ DI score at **Weeks 24, 52, 78, and 104**

Subgroup Analyses of the HAQ DI Score

To assess the generalizability of the study results, the Agency carried out subset analyses. For these analyses, we used the prespecified endpoint of HAQ-DI responders defined as those subjects with a ≥ 0.5 HAQ-DI improvement at Weeks 52 and 104. To avoid overestimating HAQ-DI responses, we used the non-responder imputation technique. For the patients in Study DE019 OLE who received adalimumab in year 1 (either 20 mg weekly or 40 mg QOW) and had a HAQ response at Week 52, 75% of these adalimumab-treated patients were responders at Week 104 (**Table 13**). For the analysis in **Table 13** and the subset analyses that follow, patients originally randomized to adalimumab 20 mg QW and those receiving 40 mg QOW are combined. The N=204 value (109 subjects from the 20 mg QW group and 95 subjects from the 40 mg QOW group, see **Table 10**) is the total number of adalimumab-treated subjects from the lead-in study who achieved a ≥ 0.5 unit HAQ DI response at Week 52 and is thus the denominator for the subgroup analyses presented below.

Table 13: Number (%) Subjects with HAQ DI ≥ 0.5 unit Response Among Week 52 Responders – Discontinued Patients Imputed as Non-Responders

Visit	Adalimumab* (N=204) n (%)
Week 104*	152 (75)

*Of patients with ≥ 0.5 unit improvement in HAQ DI, n (%) who also had ≥ 0.5 u improvement at Week 104

Subgroup analyses (Tables 14 to 24) demonstrated similar percentages of HAQ DI 0.5 unit response at Week 104 regardless of sex, race, age, weight, baseline RF positivity, duration of RA, baseline CRP, baseline TJC, baseline SJC, or baseline HAQ score though several small differences were noted.

Table 14: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response by Sex – Discontinued Patients Imputed as Non-Responders

Visit	SEX	Adalimumab (N=204) n (%)
Week 104*	**Male**	40 of 48 (83)
	Female	112 of 156 (72)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 15: Number (%) of Subjects with HAQ DI > 0.5 unit Response by Race – Discontinued Patients Imputed as Non-Responders

Visit	Race	Adalimumab (N=204), n (%)
Week 104*	White	130 of 177 (73)
	Black	9 of 11 (82)
	Asian	3 of 3 (100)
	Hispanic	7 of 11 (73)
	Others	2 of 2 (100)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 16: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response by Age – Discontinued Patients Imputed Non-Responders

Visit	Age	Adalimumab (N=204), n (%)
Week 104*	≤ 65 years	115 of 149 (77)
	> 65 years	37 of 55 (67)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 17: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response by Weight – Discontinued Patients Imputed as Non-Responders

Visit	Weight	Adalimumab (N=204), n (%)
Week 104*	≤ 70 Kg	42 of 56 (75)
	> 70 Kg	110 of 148 (74)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 18: Summary of HAQ DI ≥ 0.5 unit Responders* in the OLE Study by Weight in Quartiles at Week 104 – Discontinued Patients Imputed as Non-Responders

Observed Weight	Adalimumab (Total N=204)
0 - ≤ 64.5 kg	(N=54) n (%)
	40 (74)
> 64.5 - ≤ 75.7 kg	(N=48) n (%)
	36 (75)
> 75.7 - ≤ 90.3 kg	(N=56) n (%)
	43 (77)
> 90.3 - ≤ 154.5 kg	(N=46) n (%)
	33 (72)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 19: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response By Baseline RF – Discontinued Patients Imputed as Non-Responders

Visit	Baseline RF	Adalimumab (N=204), n (%)
Week 104*	Positive	134 of 179 (75)
	Negative	18 of 25 (69)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 20: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response By Duration of RA – Discontinued Patients Imputed as Non-Responders

Visit	Duration of RA	Adalimumab (N=204), n (%)
Week 104*	0 –2 years	19 of 24 (79)
	>2 – 5 years	37 of 44 (84)
	> 5 – 10 years	27 of 42 (64)
	> 10 years	69 of 94 (73)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 21: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response By Baseline CRP – Discontinued Patients Imputed as Non-Responders

Visit	Baseline CRP	Adalimumab (N=204), n (%)
Week 104*	Normal	55 of 75 (73)
	Abnormal	97 of 129 (75)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 22: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response By Baseline TJC – Discontinued Patients Imputed as Non-Responders

Visit	Baseline TJC	Adalimumab (N=204), n (%)
Week 104*	Value 9 - 18	43 of 53 (81)
	Value 18 - 26	46 of 60 (77)
	Value 26 - 36	38 of 50 (76)
	Value 36 - 68	25 of 41 (61)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 23: Number (%) of Subjects with HAQ DI ≥ 0.5 unit Response By Baseline SJC – Discontinued Patients Imputed as Non-Responders

Visit	Baseline SJC	Adalimumab (N=204), n (%)
Week 104*	Value 9 - 12	33 of 45 (73)
	Value 12 – 17	40 of 54 (74)
	Value 17 – 24	42 of 56 (75)
	Value 24 - 57	37 of 49 (76)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

Table 24: Number (%) of Subjects with HAQ DI ≥ 0.5 units Response By Baseline HAQ – Discontinued Patients Imputed as Non-Responders

Visit	Baseline HAQ	Adalimumab (N=204), n (%)
Week 104*	0.0 – 1.00	25 of 38 (66)
	1.00 – 1.50	50 of 57 (88)
	1.50 – 1.875	37 of 46 (80)
	1.875 – 2.875	40 of 63 (64)

*responder with ≥ 0.5 u improvement in HAQ DI score at Weeks 52 and 104

In summary, subgroup analyses of HAQ DI 0.5 unit Responders suggest that adalimumab was effective in all subgroups, regardless of demographic differences or pre-study disease activity status.

Sustained Inhibition of Structural Damage

Sustained inhibition of structural damage was measured by the Total Sharp Score (TSS), an objective measure of progression of structural damage. This was categorized by response (no change or decreased score versus increased score) between Week 52 and Week 104, and is presented in **Table 25**. A value of ≤ 0 in the TSS indicated a halt in disease progression, whereas an increased score represented disease progression and/or joint worsening. As stated previously, if ≥ 50% of subjects observed a difference of ≤ 0 units in the week 104 TSS change, or if the lower confidence limit of the observed percentage of subjects with no Week 104 TSS change was ≥ 37%, the two-year open-label TSS data would then be considered to demonstrate sustained inhibition of radiographic structural damage; these values were pre-specified by the Sponsor and agreed upon by the Agency.

Table 25: Sustained Inhibition of Structural Damage as Measured by the change in TSS between Week 52 and Week 104 (All Treated Subjects)

	Treatment Assignment in Study DE019		
	20 mg weekly (N = 165)	40 mg QOW (N = 158)	All Adalimumab (N = 323)
Total Sharp Score	n (%)	n (%)	n (%, 95% CI)
Subjects with no change or decreased score	87 (53)	88 (56)	175 (54, 49-60)
Subjects with increased score	65 (39)	64 (41)	129 (40, 35-45)
Missing	13 (8)	6 (4)	19 (6, 3-8)

QOW: every other week

At Week 104, 54% of subjects previously treated with adalimumab (20 mg weekly or 40 mg QOW) during Study DE019 had no increase in TSS (CI 49% - 60%) compared to Week 52 (**Table 25**). This result met the pre-specified endpoint of having at least 50% of subjects without radiographic progression between Week 52 and Week 104 or having the lower limit of the confidence interval for this percentage be at least 37%.

This result, using the non-responder imputation for missing data, is consistent with the conclusion of sustained inhibition of radiographic progression following two years of treatment with adalimumab. This analysis includes 19 subjects who had no x-ray analysis in Study DE019 OLE (175 of 323 total subjects).

Analysis using only the 304 (323 total minus 19 missing) subjects who had x-rays available during Study DE019 OLE resulted in a higher percentage of patients, 58% (175 of 304), with no radiographic progression. Analyzing the data by treatment allocation during Study DE019, a total of 53% (87 of 165) subjects previously treated with 20 mg adalimumab weekly had no radiographic progression and a total of 56% (88 of 158) subjects previously treated with 40 mg adalimumab QOW had no progression (**Table 25**). In summary, 54% (N=175, CI 49% - 60%) of the 323 subjects treated with adalimumab during Study DE019 had no increase in TSS at Week 104 compared to Week 52.

Secondary Efficacy Assessments

A. Number of HAQ DI Responders at 0.22, 0.50, 0.75, and 1.0 unit Levels

The number of subjects who achieved the HAQ DI 0.22, 0.50, 0.75, or 1.0 response levels was determined at Week 54 (entry for Study DE019 OLE) and at Week 104 for all treated subjects. 71%, 55%, 42%, and 24% of subjects in DE019 OLE who received adalimumab in Study DE019 had a 0.22, 0.50, 0.75, and 1.0 unit HAQ DI response (respectively) at Week 104 (**Table 26**).

Table 26: Number of Responders in the HAQ DI Levels of 0.22, 0.50, 0.75, and 1.0 (All Treated Subjects)

		Treatment Assignment in Study DE019		
		20 mg weekly (N = 165)	40 mg QOW (N = 158)	All Adalimumab (N = 323)
HAQ DI Responder Level		n (%)	n (%)	n (%)
0.22 responders	Week 54[a]	132 (80)	129 (82)	261 (81)
	Week 104	112 (68)	117 (74)	229 (71)
0.50 responders	Week 54[a]	104 (63)	95 (60)	199 (62)
	Week 104	91 (55)	88 (56)	179 (55)
0.75 responders	Week 54[a]	78 (47)	72 (46)	150 (46)
	Week 104	67 (41)	68 (43)	135 (42)
1.0 responders	Week 54[a]	52 (32)	49 (31)	101 (31)
	Week 104	40 (24)	38 (24)	78 (24)

B. Maintenance of Improved Physical Function, HAQ DI for 0.22, 0.75, and 1.0 Responders (Week 52 HAQ DI 0.22, 0.75, or 1.0 Responder Subset Subjects)

Table 27 presents the number of subjects who maintained the 0.22, 0.75, and 1.0 unit HAQ DI level of response at Week 104 after achieving that level of HAQ DI response at Week 52 (the end of lead-in Study DE019). 83%, 77%, and 59% of subjects with a 0.22, 0.75, and 1.0 unit HAQ DI level of response, respectively, at Week 52 were able to maintain that same level of response to Week 104.

Table 27: Maintenance of the HAQ DI for 0.22, 0.75, and 1.0 Responders (Week 52 HAQ DI 0.22, 0.75, or 1.0 Responder Subset Subjects)

		Treatment Assignment in Study DE019		
		20 mg weekly	40 mg QOW	All Adalimumab
HAQ DI Responder Levels		n (%)	n (%)	n (%)
0.22 Responders	Week 52	134	124	258
	Week 104	105 **(78)**	109 **(88)**	214 **(83)**
0.75 Responders	Week 52	78	71	149
	Week 104	57 **(73)**	57 **(80)**	114 **(77)**
1.0 Responders	Week 52	55	48	103
	Week 104	33 **(60)**	28 **(58)**	61 **(59)**

C. Mean HAQ DI Scores

Table 28 presents a completer analysis of mean HAQ DI scores for all treated subjects who enrolled in DE019 OLE who received adalimumab in the lead-in study. An improvement in the HAQ DI is represented by a decrease in the score. There was improvement (i.e. decrease) in mean HAQ DI scores from Week 0 to Week 54 in those subjects treated with adalimumab during Study DE019 with the mean HAQ DI score decreasing from 1.44 to 0.76 in the first year of the treatment. The mean HAQ DI score at Week 104 remained unchanged at 0.76, indicating that the group of adalimumab-treated subjects who stayed in the study maintained the HAQ DI improvement after 2 years of therapy.

Table 28: Mean HAQ DI Scores (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		All Adalimumab (N = 323)	
HAQ DI Score	N	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Week 0	165	1.44 ± 0.64	158	1.43 ± 0.63	323	1.44 ± 0.63
Week 54 [a]	161	0.76 ± 0.71	157	0.76 ± 0.66	318	0.76 ± 0.68
Week 104	146	0.79 ± 0.71	146	0.74 ± 0.65	292	0.76 ± 0.68

a Week 54 is entry visit for Study DE019 OLE
As observed data is presented
QOW: every other week, SD: standard deviation

While 323 subjects who received adalimumab in the lead-in study began Study DE019 OLE, 292 completed the study (representing a 10% drop out rate). We characterized the mean HAQ DI scores for the subjects who dropped out during the 2-year period, in order to determine whether these dropout subjects had a different response than the whole population.

Table 29 and **Table 30** list the HAQ DI scores for all treated patients and for those who dropped out before Week 104, respectively.

Subjects previously treated with placebo in the first year and adalimumab demonstrated improvement in the HAQ DI scores at Week 104 compared to Baseline - Week 0 (0.99 vs. 1.46, respectively). At Baseline (**Table 29**), the mean HAQ DI score was 1.44 for all adalimumab-treated subjects (n=323). The mean HAQ DI score decreased to 0.76 for the 292 remaining subjects in the study. For those subjects who discontinued the study before Week 104 (n=31) in **Table 30**, the mean HAQ DI score at Baseline was 1.67 and at discontinuation, it decreased to 1.06. Thus, while the mean HAQ DI score at Baseline for subjects who terminated prior to Week 104 was higher than the total group Baseline HAQ DI score (1.67 vs. 1.44), the decrease in score for subjects who terminated early was similar (0.61 vs. 0.64).

Table 29: Summary of Disability Index of the HAQ DI Score (All Treated Subjects)

		Randomized Dose in Study DE019				Study
Visit	Statistic	20mg Weekly (N=165)	40 mg QOW (N=158)	Adalimumab (N=323)	Placebo (N=134)	DE019 OLE (N=457)
Baseline	N	165	158	323	133	456
	Mean	1.44	1.43	1.44	1.46	1.45
Week 104	N	146	146	292	121	413
	Mean	0.79	0.74	0.76	0.96	0.82
Week 104 (LOCF)	N	164	158	323	134	457
	Mean	0.80	0.80	0.80	0.99	0.85

Table 30: Summary of Disability Index of the HAQ DI Score (Early Discontinuations)

Visit	Statistic	Randomized Dose in Study DE019			
		20mg Weekly (N=165)	40 mg QOW (N=158)	All Adalimumab (N=323)	Study DE019 OLE (N=457)
Termination Subjects at Baseline	N	19	12	31	31
	Mean	1.57	1.83	1.67	1.67
Subjects at Termination	N	19	12	31	31
	Mean	0.86	1.36	1.06	1.06

D. ACR Responses

The number of subjects who achieved ACR20, ACR50, and ACR70 scores at Weeks 54 and 104 are presented in **Table 31**. For each ACR measure of clinical response, similar numbers of subjects responded at both Weeks 54 and 104. 67% and 62% of all adalimumab-treated subjects achieved an ACR20 score at Weeks 54 and 104; 50% and 44% achieved an ACR50 score; and 26% and 29% achieved an ACR70 score, respectively. These data indicate that the clinically important ACR responses are consistent with the HAQ DI improvement and maintenance scores discussed earlier.

Table 31: ACR Responses (All Adalimumab-Treated Subjects) – Discontinued Subjects were Nonresponders

		Treatment Assignment in Study DE019		
		20 mg weekly (N = 165)	40 mg QOW (N = 158)	All Adalimumab (N = 323)
ACR Response		n (%)	n (%)	n (%)
ACR20 Responder	Week 54 [a]	107 (64.8)	109 (69.0)	216 **(67)**
	Week 104	99 (60.0)	101 (63.9)	200 **(62)**
ACR50 Responder	Week 54 [a]	78 (47.3)	83 (52.5)	161 **(50)**
	Week 104	67 (40.6)	75 (47.5)	142 **(44)**
ACR70 Responder	Week 54 [a]	47 (28.5)	38 (24.1)	85 **(26)**
	Week 104	45 (27.3)	47 (29.7)	92 **(29)**

a Week 54 is entry visit for Study DE019 OLE
Subjects who withdrew prematurely, or who took additional DMARDs during the study, were counted as non-responders.
As observed data is presented

The number of subjects who achieved a major clinical response, defined as having an ACR70 score for any six consecutive months between Week 0 and Week 104, was 25%. Given that ACR70 responses are very uncommon in untreated subjects, these data indicate a robust response to the study drug (**Table 32**).

Table 32: Major Clinical Response-ACR70 for Six Consecutive Months (All Treated Subjects in DE019 OLE) - LOCF

	Treatment Assignment in Study DE019		
	20 mg weekly (N = 165) n (%)	40 mg QOW (N = 158) n (%)	All Adalimumab (N = 323) n (%)
Major Clinical Response between Week 0 and Week 104	39 (23.6)	42 (26.6)	81 (25)

Subjects who withdrew prematurely, or who took additional DMARDs during the study, were counted as non-responders.
LOCF is presented
QOW: every other week

Mean values at Weeks 0, 54, and 104 for the individual components of the ACR scores are listed for all treated subjects in **Table 33**. For each of the ACR components, mean scores decreased by greater than 50% from Week 0 to 104, indicating that the benefit to adalimumab-treated patiens was a global effect, and not driven by only one or several ACR components.

Table 33: ACR Core Set of Responses (All Treated Subjects)

		Treatment Assignment in Study DE019					
		20 mg weekly (N = 165)		40 mg QOW (N = 158)		All Adalimumab (N = 323)	
ACR Parameter		*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*
TJC (0-68 joints)	Week 0	165	28.2 ± 13.7	158	27.2 ± 12.2	323	27.7 ± 12.9
	Week 54 [a]	163	10.5 ± 13.4	157	8.8 ± 11.6	320	9.7 ± 12.5
	Week 104	147	9.2 ± 12.2	146	7.7 ± 11.4	293	8.4 ± 11.8
SJC (0-66 joints)	Week 0	165	19.6 ± 9.9	158	19.4 ± 9.3	323	19.5 ± 9.6
	Week 54 [a]	163	7.9 ± 10.4	157	6.8 ± 8.4	320	7.4 ± 9.4
	Week 104	147	6.7 ± 8.6	146	5.9 ± 7.8	293	6.3 ± 8.2
Patient Global Assessment of Disease Activity (0-100 mm VAS)	Week 0	165	52.2 ± 22.7	158	53.4 ± 21.0	323	52.8 ± 21.9
	Week 54 [a]	162	25.8 ± 22.1	157	22.9 ± 19.7	319	24.4 ± 21.0
	Week 104	146	23.9 ± 21.5	146	20.6 ± 18.2	292	22.2 ± 20.0
Physician Global Assessment of Disease Activity (0-100 mm VAS)	Week 0	165	62.0 ± 16.1	158	61.7 ± 17.2	323	61.8 ± 16.6
	Week 54 [a]	162	23.5 ± 20.8	157	20.9 ± 17.3	319	22.2 ± 19.2
	Week 104	146	17.3 ± 15.7	146	18.0 ± 18.9	292	17.6 ± 17.3
Patient Assessment of Pain (0-100 mm VAS)	Week 0	165	55.0 ± 22.9	158	56.6 ± 20.4	323	55.8 ± 21.7
	Week 54 [a]	162	27.9 ± 23.8	157	23.2 ± 19.7	319	25.6 ± 22.0
	Week 104	146	24.4 ± 20.6	146	22.4 ± 19.8	292	23.4 ± 20.2
CRP (mg/dL)	Week 0	165	1.4 ± 1.4	158	1.9 ± 2.4	323	1.7 ± 2.0
	Week 54 [a]	162	0.8 ± 1.1	157	0.8 ± 1.2	319	0.8 ± 1.2
	Week 104	146	0.9 ± 2.3	145	0.7 ± 0.9	291	0.8 ± 1

a Week 54 is entry visit for Study DE019 OLE
As observed data is presented
QOW: every other week

E. Short Form-36 Questionnaire Scores

The SF-36 health related quality of life questionnaire domain scores for all treated subjects are displayed in **Table 34**. The RA guidance document specifies that for a claim of improvement in physical function, in addition to seeing an improvement in a measure of physical function (such as seen in the HAQ-DI score), there should be no worsening in health related-quality of life.

Although the LOCF method was used to impute missing data, data collection for the SF-36 questionnaire was nearly 100% (if not 100%) for each domain at Weeks 0, 52, and 104. In all domains, a > 5 point increase was seen. Similarly, > 2.5 point increases were seen in the physical and mental component summary scores, indicating improved health related-quality of life over the course of 2 years of adalimumab therapy. These levels of improvement were consistent in both the 20 mg weekly and 40 mg QOW adalimumab treatment arms.

Table 34: SF-36 Questionnaire Domain Scores (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		All Adalimumab (N = 323)	
SF-36 Parameter	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Physical Function						
Week 0	165	38.7 ± 23.1	157	40.3 ± 22.8	322	39.4 ± 22.9
Week 52	165	57.1 ± 26.5	158	57.4 ± 26.7	323	57.2 ± 26.5
Week 104	165	56.7 ± 26.2	158	58.1 ± 28.7	323	57.4 ± 27.4
Role Physical						
Week 0	165	23.5 ± 34.8	158	25.8 ± 36.4	323	24.6 ± 35.5
Week 52	165	59.0 ± 38.7	158	52.4 ± 42.6	323	55.8 ± 40.7
Week 104	165	55.2 ± 43.1	158	53.5 ± 43.3	323	54.3 ± 43.1
Bodily Pain						
Week 0	165	38.4 ± 17.2	158	37.8 ± 16.3	323	38.1 ± 16.7
Week 52	165	62.9 ± 21.3	158	63.2 ± 21.7	323	63.0 ± 21.5
Week 104	165	61.1 ± 23.1	158	62.0 ± 23.7	323	61.5 ± 23.4
General Health						
Week 0	164	50.8 ± 21.2	158	51.4 ± 19.7	322	51.1 ± 20.4
Week 52	165	63.8 ± 20.2	158	63.6 ± 20.4	323	63.7 ± 20.3
Week 104	165	62.5 ± 20.8	158	63.4 ± 21.7	323	62.9 ± 21.2
Vitality						
Week 0	164	38.0 ± 19.5	158	36.4 ± 20.8	322	37.2 ± 20.1
Week 52	165	55.5 ± 22.0	158	55.4 ± 24.1	323	55.5 ± 23.0
Week 104	165	54.8 ± 23.4	158	55.0 ± 24.2	323	54.9 ± 23.8
Social Functioning						
Week 0	165	65.2 ± 26.1	158	64.6 ± 26.6	323	64.9 ± 26.3
Week 52	165	81.4 ± 20.6	158	78.1 ± 23.0	323	79.8 ± 21.9
Week 104	165	78.2 ± 21.5	158	77.1 ± 26.7	323	77.6 ± 24.2
Role Emotional						
Week 0	165	57.8 ± 44.7	158	60.1 ± 42.1	323	58.9 ± 43.4
Week 52	165	80.0 ± 34.7	158	73.2 ± 37.9	323	76.7 ± 36.4
Week 104	165	73.9 ± 38.6	158	73.0 ± 37.8	323	73.5 ± 38.2
Mental Health						
Week 0	164	70.8 ± 18.7	158	70.1 ± 18.6	322	70.4 ± 18.7
Week 52	165	77.6 ± 17.7	158	77.3 ± 17.6	323	77.4 ± 17.7
Week 104	165	77.0 ± 16.6	158	77.8 ± 18.6	323	77.4 ± 17.6
Physical Component Summary						
Week 0	164	29.4 ± 9.0	157	29.9 ± 8.2	321	29.6 ± 8.6
Week 52	165	39.5 ± 10.6	158	39.3 ± 10.8	323	39.4 ± 10.7
Week 104	165	39.2 ± 10.6	158	39.5 ± 11.3	323	39.3 ± 11.0
Mental Component Summary						
Week 0	164	49.5 ± 12.0	157	49.0 ± 11.3	321	49.3 ± 11.6
Week 52	165	53.8 ± 10.2	158	52.6 ± 10.2	323	53.2 ± 10.2
Week 104	165	52.7 ± 9.6	158	52.5 ± 10.4	323	52.6 ± 10.0

LOCF data is presented.
QOW: every other week, LOCF: last observation carried forward, SD: standard deviation

F. Total Sharp Score (TSS)

A summary of the change of mean TSS from Week 0 to 52 (Study DE019 entry) and Week 52 to 104 (Study DE019 OLE entry) is presented in **Table 35** below. Subjects previously treated with adalimumab had mean changes in TSS from Study DE019 Baseline (Week 0) to Week 52 of -0.4. The TSS change observed in this group between Week 52 and Week 104 was 0.8. While a change in TSS of 0.8 implies a certain degree of worsening of disease score, the 0.8 value represents the change of the TSS score from Week 52 to 104. The actual mean TSS change from Baseline to Week 104 was 0.4, which is considered minimal worsening.

Table 35: Total Sharp Score (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		All Adalimumab (N = 323)	
Total Sharp Score	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Mean change from Week 0 to Week 52	152	-0.1 ± 5.7	153	-0.7 ± 7.1	305	**-0.4** ± 6.5
Mean change from Week 52 to Week 104	152	1.0 ± 8.2	152	0.6 ± 8.9	304	**0.8** ± 8.6

As observed data is presented

In contrast, subjects who received placebo in Study DE019 had a mean TSS change of 3.0 from Baseline to Week 52, and a TSS change of 3.8 from Baseline to Week 104, indicating progression of disease (**Table 36**). These subjects received placebo in DE019 and subsequently received adalimumab in Study DE019 OLE. They had a TSS change of 0.9 from Week 52 to 104, a comparable value to those subjects who were treated with adalimumab in Study DE019, indicating that adalimumab inhibited the rate of progression of structural damage similarly, despite the 1-year delay in initiating therapy.

Table 36: Summary of Change from Baseline in Modified Total Sharp Score (All Treated Subjects)

Week 104 TSS	Visit	Treatment	N	Mean	Median
Change from Baseline	Week 52	20 mg Weekly	152	-0.1	0.0
		40 mg QOW	153	-0.7	0.0
		All D2E7	305	-0.4	0.0
		Placebo	123	3.0	0.5
		DE019 OLE	428	0.6	0.0
	Week 104	20 mg Weekly	152	0.9	0.0
		40 mg QOW	152	-0.1	0.0
		All D2E7	304	0.4	0.0
		Placebo	121	3.8	0.5
		DE019 OLE	425	1.4	0.0
Change from Week 52	Week 104	20 mg Weekly	152	1.0	0.0
		40 mg QOW	152	0.6	0.0
		All D2E7	304	0.8	0.0
		Placebo	121	0.9	0.0
		DE019 OLE	425	0.8	0.0

As a point of reference, the radiographic mean changes from Week 0 to 52 from the original Study DE019 (taken from the Humira® label) are presented in **Table 37**. Subjects randomized to placebo/MTX in Study DE019 had a change in TSS of 2.7.

Table 37: Radiographic Mean Changes over 12 Months (Study DE019), from the Humira® Label

	Placebo/MTX	Humira/MTX	Placebo/MTX – Humira/MTX (95% CI)*	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% CI for the differences in change in scores between MTX and Humira®
**Based on rank analysis

G. Yearly Progression in Total Sharp Score

Table 38 displays the estimated and actual yearly progression of the TSS for all treated subjects. The estimated yearly progression (based on individual subjects' baseline scores and estimates of their duration of disease) of TSS for all adalimumab-treated subjects was 6.88, while the actual progression of TSS was -0.37 for Weeks 0 to 52 and 0.21 for Weeks 52 to 104, respectively.

Table 38: Yearly Progression of TSS (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		Adalimumab (N = 323)	
Yearly Progression	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**N**	**Mean ± SD**
Estimated Yearly Progression	151	7.13 ± 12.20	153	6.64 ± 8.33	304	**6.88** ± 10.42
Actual Progression during Study DE019	152	-0.09 ± 5.71	153	-0.64 ± 7.11	305	**-0.37** ± 6.44
Actual Progression during Study DE019 OLE	152	0.45 ± 4.63	152	-0.03 ± 3.75	304	**0.21** ± 4.22
Difference between Estimated and Actual Progression during Study DE019 OLE	151	-6.69 ± 12.91	152	-6.69 ± 9.08	303	-6.69 ± 11.14

As observed data is presented

H. Erosion Score

A summary of the change of mean erosion score from Study DE019 entry and Study DE019 OLE entry is presented in **Table 39**. Subjects previously treated with adalimumab had mean changes in erosions of -0.3 from Week 0 to Week 52. The mean change seen between Weeks 52 and 104 was 0.3.

Table 39: Mean Change in Erosion Score (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		Adalimumab (N = 323)	
Erosions	***n***	***Mean ± SD***	***n***	***Mean ± SD***	***n***	***Mean ± SD***
Mean change from Week 0 to Week 52	152	-0.2 ± 2.7	153	-0.4 ± 4.0	305	**-0.3** ± 3.4
Mean change from Week 52 to Week 104	152	0.5 ± 5.0	152	0.2 ± 4.9	304	**0.3** ± 5.0

As observed data is presented
QOW: every other week, SD: standard deviation

In contrast, placebo subjects had mean changes in erosion scores of 1.6 and 0.1 in respective time periods (**Table 40** and **Table 41**).

Table 40: Summary of Actual Erosion Scores (All Treated Subjects)

		Randomized Dose in DE019				
	Statistics	20 mg QW (N=165)	40 mg QOW (N=158)	Adalimumab (N=323)	Placebo (N=134)	DE019 OLE (N=457)
Baseline						
	N	152	153	305	123	428
	Mean	24.6	27.6	**26.1**	**22.7**	25.1
	Median	17.51	19.0	18.0	14.5	17.5
Last Visit in De019 (Week 52)						
	N	152	153	305	123	428
	Mean	24.4	27.3	**25.8**	**24.3**	25.4
	Median	17.0	20.0	18.0	17.5	18.0
Week 104						
	N	152	152	304	121	425
	Mean	24.8	27.6	**26.2**	**24.3**	25.7
	Median	17.0	19.8	18.5	17.0	18.5

Table 41: Summary of Change from Baseline in Erosion Score (All Treated Subjects)

	Visit	Treatment	N	Mean	Median
Change from Baseline					
	Last Visit in DE019 (Week 52)	20 mg weekly	152	-0.2	0.0
		40 mg QOW	153	-0.4	0.0
		Adalimumab	**305**	**-0.3**	0.0
		Placebo	**123**	**1.6**	0.5
		DE019 OLE	428	0.2	0.0
	Week 104	20 mg weekly	152	0.3	0.0
		40 mg QOW	152	-0.2	0.0
		Adalimumab	**304**	**0.0**	0.0
		Placebo	**121**	**1.6**	0.5
		DE019 OLE	425	0.5	0.0
Change from Week 52					
	Week 104	20 mg weekly	152	0.5	0.0
		40 mg QOW	152	0.2	0.0
		Adalimumab	**304**	**0.3**	0.0
		Placebo	**121**	**0.1**	0.0
		DE019 OLE	425	0.3	0.0

The erosion score change of 0.3 for Weeks 52 to 104 for the adalimumab-treated subjects suggests a worsening of disease, but in similar fashion to the interpretation of the TSS change, the change of 0 over the two years of the trial does not indicate any acceleration of erosions.

I. No Erosion Score Change Between Week 52 and Week 104

The number of subjects with various changes in erosion score between Weeks 52 and 104 is presented in **Table 42**. At Week 104, 64% of subjects (206 of 323) previously treated with adalimumab had either no change or a lower erosion score compared to Week 52. 30% of subjects (98 of 323) previously treated with adalimumab developed increased erosion scores between Weeks 52 and 104. Of these, 64% of subjects (63 of 98) developed a change in erosion score between 0.5 and 1.

Of subjects treated with placebo, a total of 58% (77 of 135 subjects) had either no change or a decrease in erosion score at Week 104, and 33% (44 of 134) had a worsening score.

Table 42: Number of Subjects by Erosion Score Change Between Week 52 and Week 104 (All Treated Subjects)

	Treatment Assignment in Study DE019		
Change in Erosion Score at Week 104	**20 mg weekly (N = 165) n (%)**	**40 mg QOW (N = 158) n (%)**	**All Adalimumab (N = 323) n (%)**
Less than zero	43 (26)	55 (35)	98 (30)
Equal to zero	60 (36)	48 (30)	108 (33)
0.5 - 1	34 (21)	29 (18)	63 (20)
1.5 - 2	10 (6)	10 (6)	20 (6)
Greater than 2	5 (3)	10 (6)	15 (5)
Missing	13 (8)	6 (4)	19 (6)

As observed data is presented
QOW: every other week

In summary, of the subjects treated with adalimumab in Study DE019 OLE, 64% had either no change or a decrease in erosion score.

J. Subgroup Analysis of Subjects with Change of Less Than or Equal to Zero in Erosion Score at Week 52 and Followed to Week 104

All subjects with a change of less than or equal to zero in erosion score at Week 52 (relative to the beginning of Study DE019) were followed to week 104 to determine whether their erosion score increased. A summary of subjects with changes in erosion score is presented in **Table 43**.

66% (132 of 200 subjects) previously treated with adalimumab, who had a change of less than or equal to zero in erosion score at Week 52, did not increase their erosion score at Week 104.

Table 43: Subjects with No New Erosions (at Week 52 Subset)

	Treatment Assignment in Study DE019		
	20 mg weekly	40 mg QOW	All Adalimumab
Erosions	n (%)	n (%)	n (%)
Erosion score change ≤0 at Week 52	101	99	200
Equal to Zero	68 (67)	64 (65)	132 (**66**)
Greater than Zero	33 (33)	34 (34)	67 (34)
Missing	0 (0)	1 (1)	1 (<1)

As observed data is presented
QOW: every other week

K. Joint Space Narrowing

Joint space narrowing (JSN) scores for all adalimumab-treated subjects are presented in **Table 44**. The mean change in JSN score was -0.1 from Weeks 0 to 52, and was 0.5 from Weeks 52 to 104.

Table 44: Joint Space Narrowing Score (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg QOW (N = 158)		All Adalimumab (N = 323)	
Joint Space Narrowing	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Mean change from Week 0 to Week 52	152	0.1 ± 3.6	153	-0.3 ± 3.5	305	**-0.1** ± 3.6
Mean change from Week 52 to Week 104	152	0.6 ± 3.4	152	0.4 ± 4.4	304	**0.5** ± 3.9

As observed data is presented

The actual JSN scores from Baseline to Week 104 are listed in **Table 45.** This table confirms the mean change in score of 0.5 units from Baseline to Week 104 for all adalimumab-treated subjects. In this same period, JSN scores increased 2.4 units from a score of 22.1 (at Baseline) to 24.5 (at Week 104) for patients randomized to placebo during the blinded lead-in study. The JSN scores are consistent with erosion scores and TSS during the same time periods and indicate continued inhibition of progression of joint space narrowing.

Table 45: Summary of Joint Space Narrowing Score (All Treated Subjects)

		Randomized Dose in Study DE019				Study
Visit	Statistic	20mg Weekly (N=165)	40 mg QOW (N=158)	All Adalimumab (N=323)	Placebo (N=134)	DE019 OLE (N=457)
Baseline	N	152	153	305	123	428
	Mean	24.4	24.8	24.6	22.1	23.9
Last Visit in DE019 (Week 52)	N	152	153	305	123	428
	Mean	24.6	24.5	24.6	23.6	24.3
Week 104	N	152	152	304	121	425
	Mean	25.1	25.1	25.1	24.5	24.9

L. Subgroup Analyses of Subjects with No X-Ray Progression, by Full Analysis Set

The following section presents analyses of the full analysis set for those subjects with no x-ray progression at Week 104, defined as those subjects with a Sharp score change of ≤ 0 compared to the Week 0 Baseline. As shown in **Table 46**, a higher proportion of subjects (55%, 177 of 323) treated with adalimumab in Study DE019 had a Sharp score change of ≤ 0 at Week 104 than subjects who received placebo (42%) in the randomized portion of the study.

Table 46: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) At Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set (Nonresponder Imputation)

Change in Sharp Score	Adalimumab (N=323)	Placebo (N=134)
Change ≤ 0	177 (55)	56 (42)

Subgroup analysis by sex (**Table 47**) displays a small advantage of adalimumab for males over females (63% vs. 52%, respectively) for Sharp score changes of ≤ 0.

Table 47: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) At Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By Sex (Nonresponder Imputation)

SEX	Change in Sharp Score	Adalimumab (N=323)	Placebo (N=134)
Female	Change ≤ 0	128 (52)	43 (45)
Male	Change ≤ 0	49 (63)	13 (33)

For all racial subgroups (**Table 48**), the proportion of subjects with no x-ray progression was favorable and comparable, though there were few Asians, Hispanics, and subjects listed as "Other" ethnic groups.

Table 48: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) At Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By Race (Nonresponder Imputation)

RACE	Adalimumab (N=323)
Asian	4 (67)
Black	13 (65)
Hispanic	6 (40)
Others	3 (75)
White	151 (54)

Table 49 presents the number of subjects with no x-ray progression by whether or not they were ≤ 65 or > 65 years of age at the beginning of Study DE019. Adalimumab-treated subjects who were ≤ 65 years of age fared slightly better (57%) than those aged > 65 years (48%).

Table 49: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By Age (Nonresponder Imputation)

AGE	Adalimumab (N=323)
Age ≤ 65	132 (57)
Age > 65	45 (48)

The number of subjects with no x-ray progression was analyzed as a function of subjects' weight (**Table 50**). Subjects had comparable proportions with no x-ray progression regardless of weight class.

Table 50: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Scpre Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By Weight (Nonresponder Imputation)

WEIGHT	Adalimumab (N=323)
Weight ≤ 70 Kg	64 (52)
Weight > 70 Kg	113 (57)

The numbers of subjects with no x-ray progression are presented according to the duration of RA in **Table 51**. RA subjects had comparable percentages with no x-ray progression irrespective of the duration of RA in Study DE019 OLE.

Table 51: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By Duration of RA (Nonresponder Imputation)

Duration of RA	Adalimumab (N=323)
0-2 years	55 (51)
2-5 years	41 (60)
5-10 years	81 (55)

Table 52 presents the number of subjects with no x-ray progression according to the status of rheumatoid factor at study entry. Comparable percentages of patients had no x-ray progression at Week 104 regardless of RF status. This finding is clinically important because RF positive subjects typically have more aggressive underlying disease than RF negative subjects.

Table 52: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By RF Status (Nonresponder Imputation)

RF Status	Adalimumab (N=323)
Negative	30 (54)
Positive	147 (55)

Adalimumab-treated subjects had similar percentages of subjects with no x-ray progression regardless of initial CRP level (**Table 53**).

Table 53: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By CRP (Nonresponder Imputation)

CRP	Adalimumab (N=323)
CRP Abnormal	103 (53)
CRP Normal	74 (57)

The number of subjects with no x-ray progression were analyzed according to the number of tender joints (**Table 54**) or swollen joints (**Table 55**), presented in quartiles. Overall, there were no trends indicating a better or worse effect of adalimumab based on subjects' TJC or SJC.

Table 54: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE – Full Analysis Set By TJC by Quartiles (Nonresponder Imputation)

TJC by Quartiles	Adalimumab (N=323)
Quartile 1 (≤ 15)	32 (58)
Quartile 2 (15-21)	35 (59)
Quartile 3 (21-27)	28 (41)
Quartile 4 (>27)	82 (59)

Table 55: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Score Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline – Full Analysis Set By SJC (Nonresponder Imputation)

SJC	Adalimumab (N=323)
Quartile 1 (≤ 11)	29 (55)
Quartile 2 (11-14)	34 (58)
Quartile 3 (14-18)	32 (52)
Quartile 4 (>18)	82 (55)

Presented by HAQ score quartiles (**Table 56**), adalimumab-treated subjects had similar rates of no x-ray progression, though subjects with the highest quartile HAQ scores had a slight drop compared to the other 3 quartiles (46% vs. 61%, 58, and 68%).

Table 56: Number (%) of Subjects with No X-Ray Progression (Defined as Sharp Change ≤ 0) at Week 104 in Study DE019 OLE Compared to Baseline– Full Analysis Set By HAQ (Nonresponder Imputation)

HAQ	Adalimumab (N=323)
Quartile 1 (≤ 0.875)	38 (61)
Quartile 2 (0.875 – 1.25)	35 (58)
Quartile 3 (1.25 – 1.625)	38 (68)
Quartile 4 (>1.625)	66 (46)

In summary, these analyses did not identify any subgroups of subjects with acceleration of structural damage in the second year of adalimumab treatment.

6.1.5 Clinical Microbiology

There were no clinical microbiology issues to discuss in this submission.

6.1.6 Efficacy Conclusions

The two pre-specified efficacy objectives were to determine whether adalimumab was able to maintain improved physical function and sustain inhibition of structural damage for subjects who received adalimumab in the lead-in Study DE019.

As such, patients who achieved a $\geq$ 0.5 unit improvement at Week 52 and were able to maintain that improvement to Week 104 were considered HAQ DI responders. Using LOCF, 82% of all adalimumab-treated subjects achieved this endpoint. Using nonresponder imputation, 75% of all adalimumab-treated subjects achieved this endpoint.

Other clinical analyses, including the proportion of HAQ DI 0.22, 0.75, and 1.0 responders, the proportion of ACR20, ACR50, and ACR70 responders, were consistent with this endpoint of subjects able to maintain improved physical function. Subgroup analyses showed no significant differences in the level of HAQ DI response seen.

In support of the objective of sustained inhibition of radiographic progression, at Week 104, 54% of adalimumab-treated patients in Study DE019 had no increase in their TSS compared to Week 52. TSS data at Week 104 showed similar results in subjects previously randomized to adalimumab, as well as those previously randomized to placebo in the lead-in study, indicative of the benefits of the open-label administration of adalimumab in Study DE019 OLE.

Secondary efficacy assessments, as well as quality of life assessments, were consistent with the two primary efficacy assessments.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Three subjects died during Study DE019 OLE (**Table 57**).

Table 57: Deaths in Study DE019 OLE

Age, Sex	AE	Day of death in OLE Study	Study DE019 assignment
65, M	Interstitial pneumonia	83	Placebo
77, F	Fever, sepsis	492	20 mg weekly
55, F	Small bowel infarction s/p Myocardial infarction	394	20 mg weekly

Brief narratives of the deaths in Study DE019 OLE are as follows:

A 65 y.o. male with a 13 year history of RA died on Day 83 of exposure to open-label adalimumab (received placebo during the double-blind phase of lead-in Study DE019). His past medical history was significant for hypothyroidism, coronary artery disease, previous myocardial infarction, a post-inflammatory pulmonary fibrosis. After developing acute respiratory distress on Day 59 of adalimumab exposure, symptoms resolved until Day 83 of exposure to adalimumab when he developed interstitial pneumonia and died 11 days later.

A 77 y.o. female with a 6 year history of RA died on Day 492 of adalimumab exposure with a diagnosis of sepsis after presenting with fever and confusion. She had a medical history significant for hypertension, congestive heart failure, and osteoporosis. She previously received adalimumab 20 mg weekly in the lead-in study.

A 55 y.o. female with a 16 year history of RA died on Day 405 of adalimumab due to small bowel infarction after presenting with a myocardial infarction and abdominal pain. She had a history of hypertension, peripheral vascular disease, coronary artery disease, and hyperlipidemia; she received adalimumab 20 mg weekly in the lead-in study.

These three deaths in Study DE019 OLE do not suggest a serious safety signal given their small numbers. In comparison, a total of 3 (0.5%) of 619 patients died of AE's in the placebo-controlled period of lead-in Study DE019. The underlying types of illnesses associated with the deaths in Study DE019 OLE, i.e. infectious and cardiovascular, are common in the older RA population. However, given the association of adalimumab use with serious infections, the possibility of a contribution of adalimumab to the infection-related deaths cannot be ruled out.

7.1.2 Other Serious Adverse Events

Malignancies and Serious Infectious Adverse Events

Out of 457 subjects, 9 (2%) had 10 malignancies which occurred between the first dose of OLE treatment and < 70 days after the last dose (8 adalimumab-treated subjects vs. 1 placebo subject), **Table 58**. One patient had left and right breast carcinomas that counted as two events. Four malignancies were deemed of life-threatening severity (breast carcinoma, colon carcinoma, Hodgkin's disease, and malignant lymphoma). The most frequently reported malignancy was skin carcinoma (3 of 457 subjects, 0.7%).

Table 58: Listing of Malignancies in Study DE019 OLE

Age	HARTS Term (Investigator Term)	Days on Drug	Severity	Relationship
67	Breast carcinoma	478	Life-threatening	Unlikely
66	Basal cell carcinoma	382	Mild	Unlikely
64	Colon cancer	95	Life-threatening	Unlikely
68	Basal cell carcinoma	408	Severe	Unrelated
73	Squamous cell carcinoma (hip)	567	Mild	Unlikely
72	Hodgkin's disease	584	Life-threatening	Probable
52	Cervical carcinoma (stage I)	540	Severe	Possible
56	Squamous cell carcinoma (mouth)	562	Mild	Unrelated
72	Malignant lymphoma	468	Life-threatening	Unlikely

The listing of serious infectious AEs (any infection that resulted in subject hospitalization or required treatment with iv antibiotics) that occurred in Study DE019 OLE is presented in **Table 59**. A total of 17 subjects (3.7% of 457) reported 21 serious infectious AEs in the open-label study. Of this total, 14 subjects had 18 AEs that were treatment-emergent and 3 AEs that were post-treatment. In the double-blind study, a comparable 16 of 419 subjects (3.8%) in the adalimumab group had serious infectious AEs. The most common serious infectious AEs in the open-label study were 5 cases of pneumonia and 2 cases of infection and sepsis each. Three cases of granulomatous infections were seen in the open-label phase of adalimumab treatment (one case of tuberculosis and two cases of histoplasmosis). This is in comparison to two cases of granulomatous infections seen in the double-blind phase: one case of primary tuberculosis (of the cervical lymph nodes – scrofula) and one case of histoplasmosis. The serious infections observed in Study DE019 OLE appear generally consistent with what is reflected in the current Humira® label.

Table 59: Listing of Serious Infectious Adverse Events in Study DE019 OLE

Body System (n total)	HARTS Term	Adalimumab 40mg QOW (N=457) n
Body as a Whole (4)	Infection	2
	Sepsis	2
Digestive System (2)	Gastroenteritis	1
	Gastrointestinal disorder	1
Respiratory System (7)	Bronchitis	1
	Interstitial pneumonia	1
	Pneumonia	5
Skin and Appendages (1)	Herpes Zoster	1
Urogenital System (2)	Pyelonephritis	1
	Urinary tract infection	1

Table 60 displays the incidence of cancer and serious infections encountered in 6 month intervals for both Studies DE019 and DE019 OLE. Subjects listed from 12-18 months and 18-24 months all received adalimumab 40 mg QOW but are listed under which treatment they received in the double-blind portion of the lead-in study.

The number of serious infectious AEs was higher in months 12-18 (8.83 events/100 pt-yrs) compared to months 0-6 (4.09 events/100 pt-yrs) for the 20 mg Weekly dose group. But for the all adalimumab-treated group as a whole, there was a comparable number of events in months 12-18 compared to months 0-6 (7.63 vs. 7.33/100 pt-yrs). While the rates of serious infections are consistently higher in the adalimumab group than placebo, the data do not provide evidence of acceleration in the rate of serious infections with longer duration of adalimumab exposure.

The number of malignancies including lymphoma was higher in months 12-18 for all adalimumab-treated subjects as a whole (5.09 events/100 pt-yrs), compared to earlier study periods (2.62 events/100 pt-yrs in months 0-6 and 1.78 events/100 pt-yrs in months 6-12). However, no malignancies were seen in the months 18-24. Thus, there was no evidence of an acceleration in the rate of malignancy with longer exposure to adalimumab.

It is surprising that no serious infectious AEs or malignancies were reported during months 18-24 in Study DE019 OLE (in either the 20 mg weekly group or the 40 mg QOW group). The Sponsor verified on two separate occasions that no serious infectious AEs or malignancies were seen during months 18 to 24. Review at the time of the initial licensure of adalimumab documented the occurrence of serious infections. Consequently, a boxed warning was included in the Humira® label warning of the occurrence of TB in adalimumab-treated patients and recommended screening and prophylaxis for latent tuberculosis infection. The Humira® label also includes a bold warning of serious infections and sepsis, including fatalities, as well as tuberculosis and opportunistic fungal infections. The Infections section of the adverse reaction section of the Humira® label states that serious infections occurred at a rate of 0.04 per patient-year in adalimumab-treated patients compared to 0.02 per patient-year in placebo controls.

Table 60: Incidence of Cancers and Serious Infections, by 6-Month Periods in Studies DE019 and DE019 OLE

Interval	***Lead-in Study DE019*** **AE Category**	**20 mg Qwk (N=212)** n(n*100/PYs)	**40 mg QOW (N=207)** n(n*100/PYs)	**Adalimumab (N=419)** n(n*100/PYs)	**Placebo (N=200)** n(n*100/PYs)
0 – 6 Months	Patient Years (PYs)	97.8	93.1	190.9	84.7
	Any Serious Infectious AE	4 (4.09)	10 (10.74)	14 (7.33)	0 (0)
	Any AE of Malignancies (including lymphoma)	4 (4.09)	1 (1.07)	5 (2.62)	1 (1.18)
6-12 Months	Patient Years (PYs)	86	82.5	168.5	72.1
	Any Serious Infectious AE	1 (1.16)	3 (3.64)	4 (2.37)	1 (1.39)
	Any AE of Malignancies (including lymphoma)	1 (1.16)	2 (2.42)	3 (1.78)	0 (0)
Interval	***Study DE019 OLE*** AE Category	**20 mg Qwk (N=165)** n(n*100/PYs)	**40 mg QOW (N=158)** n(n*100/PYs)	**Adalimumab (N=323)** n(n*100/PYs)	**Placebo (N=134)** n(n*100/PYs)
12-18 Months	Patient Years (PYs)	79.3	78	157.3	64.6
	Any Serious Infectious AE	7 (8.83)	5 (6.41)	12 (7.63)	5 (7.74)
	Any AE of Malignancies (including lymphoma)	5 (6.31)	3 (3.85)	8 (5.09)	1 (1.55)
18-24 Months	Patient Years (PYs)	74.7	74.6	149.3	62
	Any Serious Infectious AE	0 (0)	0 (0)	0 (0)	0 (0)
	Any AE of Malignancies (including lymphoma)	0 (0)	0 (0)	0 (0)	0 (0)

Serious Adverse Events

Table 61 lists the number of SAEs in Study DE019 OLE by body system and by HARTS term. The most frequently reported SAEs, in descending order, were clinical flare reaction, surgery, pneumonia, myocardial infarction, and joint disorder.

Table 61: Listing of Serious Adverse Events in Study DE019 OLE (Safety Set)

Body System (n total)	HARTS Term	Adalimumab 40 mg QOW (N=457) n
Body as a Whole (24)	Accidental injury	2
	Adenoma	2
	Clinical flare reaction	7
	Fever	1
	Infection	2
	Neoplasm	1
	Pain in extremity	1
	Sepsis	2
	Surgery	7
Cardiovascular System (15)	Angina pectoris	1
	Atrial fibrillation	1
	Atrial flutter	1
	Cardiovascular disorder	2
	Cerebrovascular accident	1
	Chest pain	2
	Congestive heart failure	1
	Coronary artery disorder	2
	Heart block	1
	Left heart failure	1
	Myocardial infarct	4
	Syncope	1
	Vascular aneurysm	1
Digestive System (11)	Abnormal stools	1
	Cholecystitis	1
	Diarrhea	1
	Gastritis	1
	Gastroenteritis	2
	Gastrointestinal carcinoma	1
	Gastrointestinal disorder	3
	Ileus	1
	Intestinal obstruction	1
Heme and Lymphatic System (1)	Lymphoma like reaction	1
Metabolic/Nutritional System (2)	Dehydration	1
	Hyponatremia	1
Musculoskeletal System (13)	Arthralgia	1
	Arthritis	3
	Arthrosis	2
	Bone fracture (not spontaneous)	3
	Joint disorder	4
Nervous System (3)	Confusion	1
	Depression	1
	Multiple sclerosis	1
Respiratory System (10)	Bronchitis	1
	Dyspnea	1
	Emphysema	1
	Interstitial pneumonia	1
	Lung disorder	2
	Pneumonia	5
	Respiratory disorder	1
Skin and Appendages (3)	Breast carcinoma	1
	Herpes Zoster	1
	Skin carcinoma	1
Urogenital System (4)	Cervical carcinoma	1
	Menorrhagia	1
	Pyelonephritis	1
	Urinary tract infection	1

One 55 y.o. female entered study DE019 OLE with an MRI consistent with multiple sclerosis. After 589 days on adalimumab, she was diagnosed with central demyelination-(MS) like illness. During the first year of double-blind treatment, there was one subject who was diagnosed on Study Day 29 with a central demyelination-(MS) like illness. While serious, demyelination-like illnesses are uncommon occurrences and have been reported before in both clinical trials and post-marketing experience with TNF blocking agents.

The Humira® package insert contains information on serious infections, neurologic events including demyelinating disease, hypersensitivity reactions, cytopenias, lupus-like syndrome, and lymphomas based on analysis of the serious adverse events submitted at the time of the initial BLA. The SAEs reported in Study DE019 OLE do not indicate any new safety concerns compared to what is currently included in the Humira® label.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 415 of 457 (91%) subjects completed Study DE019 OLE. 42 of 457 (9%) subjects prematurely withdrew from the study (**Table 62**). Of these, 19 withdrew due to an AE; 8 subjects withdrew due to lack of efficacy and/or progression of study disease; 5 subjects withdrew due to withdrawal of consent; 4 subjects were lost to follow up; 3 subjects died; 2 subjects withdrew due to administrative reasons; and 2 subjects withdrew due to protocol deviations.

Table 62: Summary of Subject Final Status (All Treated Subjects)

	Adalimumab 40 mg QOW (N=457) n (%)
Full Analysis Set	457 (100)
Completed 104 week study	415 (91)
Early Discontinuation	42 (9)
Discontinuations Due To:	
Adverse Event	19 (4)
Lost to Follow-Up	4 (1)
Protocol Violation	2 (<1)
Death	2 (<1)[a]
Withdrawal of Consent	5 (1)
Lack of Efficacy and/or Progression Of Study Disease	8 (2)
Administrative Reasons	2 (<1)

[a]an additional subject died, listed as due to an AE for a total of 3 deaths

7.1.3.2 Adverse events associated with dropouts

Table 63 displays the treatment-emergent AEs that resulted in the 19 patients (4.2% of 457) who dropped out of Study DE019 OLE. 11 subjects withdrew due to AEs deemed at least possibly related to study drug. Five subjects wihdrew due to cancer (breast CA, colon CA, cervical CA, lymphoma and Hodgkin's lymphoma). Four subjects withdrew because of infectious AEs (2 with pneumonia, one also reported as histoplasmosis), tuberculosis, and sepsis.

Table 63: Subjects with Treatment-Emergent Adverse Events Resulting in Withdrawal (Safety Set)[a]

Age	Sex	Adverse Event HARTS Term (Investigator Term)	Day on Drug At Onset	Duration (days)	Severity	Relationship[b]	Outcome
59	F	Infection (tuberculosis)	396	220	Severe	Possible	Resolved
54	F	Multiple sclerosis	589	-	Severe	Possible	Not resolving
67	F	Breast carcinoma (left breast) Breast carcinoma (right breast)	478 478	- -	Life-threatening Life-threatening	Unlikely Unlikely	Not resolving Not resolving
44	F	Infection (histoplasmosis) Pneumonia (worsening secondary to histoplasmosis)	649 649	189 189	Severe severe	Possible possible	Resolved Resolved
77	F	Fever Sepsis confusion	492 492 492	10 10 10	Life-threatening	Possible	Fatal
73	F	Purpura (steroid purpura) Angioedema (swollen tongue) Pruritus (itching) Urticaria	18 18 18 18	38 9 24 14	Moderate Moderate Moderate Moderate	Unrelated Probable Probable Probable	Resolved Resolved Resolved Resolved
65	F	Pneumonia	597	59	Moderate	Unlikely	Resolved
83	F	Maculopapular rash	687	-	Severe	Possible	Resolving
64	F	Gastrointestinal carcinoma (colon CA)	95	82	Life-threatening	Unlikely	Resolved
51	F	Injection site pain (pain around abdomen injection site)	85	1	Moderate	Unrelated	Resolved
72	M	Lymphadenopathy (aortocaval adenopathy)	584	-	Severe	Probable	Not resolving
60	F	Clinical flare reaction (RA flare)	389	-	Severe	Unrelated	Not resolving
58	F	Hypesthesia (numbness/hands, feet, lips)	386	-	Moderate	Possible	Resolving
52	F	Cervical CA (stage 1)	540	95	Severe	Possible	Resolved
66	M	Coronary artery disorder (CAD)	724	2	Life-threatening	Unlikely	Resolved
63	F	Leucopenia	363	56	Mild	Possible	Resolved
72	F	Neoplasm (malignant lymphoma)	468	-	Life-threatening	Unlikely	Not resolving
70	F	Lung disorder (left apical lung lesions) Skin nodule (right axillary nodule)	69 69	136 -	Severe severe	Unrelated Unrelated	Resolved Not resolving
52	M	Platelet count decreased	183	-	Moderate	Possible	Not resolving

a Treatment-emergent AEs defined as those that occurred between first dose of open-label treatment and < 70 days after the last dose.
b Relationship to study drug was determined by the Investigator.

Nearly all of the AEs were at least moderate in severity, though the individual listings of AEs have previously been reported in association with TNF-blocker administration.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Beginning at Week 54 (after a 2 week screening period from the original double-blind placebo-controlled study), subjects had evaluations every 6 weeks up to Week 66 for vital signs, concomitant medications, ACR parameters, disability index of the HAQ/VAS, general laboratory, and any adverse events. From Week 66 to Week 104, these evaluations were performed every 12 weeks. Standard case report forms were used to record any adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were deemed to be appropriate. Treatment emergent adverse events were reported using HARTS body system/preferred term classification. Individual AEs for Study DE019 OLE are summarized by (1) body system and preferred term, body system, (2) by body system, preferred term, and closest relationship to study drug as assessed by the Investigators, and (3) by body system, preferred term, and highest severity (intensity).

7.1.5.3 Incidence of common adverse events

The incidence of common adverse events in this study was compared to those AEs seen in patients receiving adalimumab vs. placebo in the original lead-in study.

7.1.5.4 Common adverse event tables

The most frequently reported treatment-emergent AEs (i.e. those occurring in $\geq$ 5% of subjects) during Study DE019 OLE are presented in **Table 64**, with comparison to similar data from the lead-in double-blinded study (Study DE019) for all subjects who received adalimumab. A comparable percentage of subjects in the open-label study reported treatment-emergent AEs compared to the lead-in study for AEs occurring in $\geq$ 5% of subjects. One exception was for the AE of "clinical flare reaction", reported by 14% of previously treated adalimumab subjects in the OLE study vs. 5% during the blinded first year of adalimumab therapy.

Table 64: Number (%) of Subjects with Most Frequently Reported (≥ 5 % of Subjects) Treatment Emergent Adverse Events in Study DE019 OLE (Safety Set)

Treatment-Emergent [a] Adverse Event[b,c]	Study DE019 OLE Prior Adalimumab (N=323) n (%)	Study DE019 OLE Prior Placebo (N=134) n (%)	Study DE019 OLE All Subjects (N=457) n (%)	Study DE019 All Adalimumab (N=419) n (%)
Upper respiratory infection	48 (15)	18 (13)	66 (14)	82 (20)
Rhinitis	38 (12)	18 (13)	56 (12)	71 (17)
Clinical flare reaction	45 (14)	9 (7)	54 (12)	20 (5)
Accidental injury	39 (12)	14 (10)	53 (12)	57 (14)
Sinusitis	30 (9)	21 (16)	51 (11)	64 (15)
Arthralgia	27 (8)	8 (6)	35 (8)	43 (10)
Joint disorder	25 (8)	5 (4)	30 (7)	27 (6)
Flu syndrome	20 (6)	10 (8)	30 (7)	21 (5)
Urinary tract infection	22 (7)	7 (5)	29 (6)	38 (9)
Bronchitis	21 (7)	7 (5)	28 (6)	29 (7)
Infection	13 (4)	12 (9)	25 (6)	48 (12)
Rash	15 (5)	10 (8)	25 (6)	42 (10)
Hypertension	16 (5)	8 (6)	24 (5)	28 (7)
Asthenia	16 (5)	7 (5)	23 (5)	32 (8)
Back pain	16 (5)	7 (5)	23 (5)	32 (8)
Surgery	18 (6)	5 (4)	23 (5)	25 (6)

Table 65 provides an overview of the number of patients in both Studies DE019 and DE019 OLE with treatment-emergent AEs, expressed in number of events per 100 patient-years of exposure. In all categories of AEs, the number of events per 100 patient-years of exposure in the open-label extension study were comparable, if not less, than the event rates seen in the double-blind portion of the lead-in study.

Taken together, data from **Table 64** and **Table 65** suggest that receiving adalimumab treatment for an additional year in open-label fashion did not increase the rate of overall AEs.

Table 65: Overview of Number of Treatment-Emergent Adverse Events In Study DE019 and In Open Label Study DE019 OLE (Safety Set)

	Double-Blind Lead-In Study DE019				Study DE019 OLE
Adverse events category[a]	**20 mg Wk (N=212) (PYs=186.7) n(#/100PYs)**	**40 mg EOW (N=207) (PYs=179.2) n(#/100PYs)**	**D2E7 ALL (N=419) (PYs=365.9) n(#/100PYs)**	**Placebo (N=200) (PYs=161.3) n(#/100PYs)**	**40 mg QOW (N =457) (PYs=433.3) n(#/100PYs)**
Any AE	1291 (691.5)	1273 (710.3)	2564 (700.7)	1210 (750.1)	1868 (431.1)
Any Serious AE	43 (23.0)	40 (22.3)	83 (22.7)	27 (16.7)	95 (21.9)
Any Severe AE	89 (47.7)	90 (50.2)	179 (48.9)	66 (40.9)	150 (34.6)
Any at least possibly drug-related AE	353 (189.1)	375 (209.2)	728 (199.0)	336 (208.3)	302 (69.7)
Any AE leading to death	1 (0.5)	5 (2.8)	6 (1.6)	0 (0)	5 (1.2)
Any AE leading to withdrawal	27 (14.5)	51 (28.5)	78 (21.3)	27 (16.7)	26 (6.0)
Any AE resulting in dose interruption	99 (53.0)	75 (41.8)	374 (47.6)	79 (49.0)	123 (28.4)
Any infectious AE	279 (149.4)	252 (140.6)	531 (145.1)	190 (117.8)	446 (102.9)
Any Serious Infectious AE	5 (2.7)	13 (7.3)	18 (4.9)	1 (0.6)	17 (3.9)
Any AE of Skin Reaction	103 (55.2)	156 (87.0)	259 (70.8)	172 (106.6)	N/A
Any AE of Immunologic Reaction	1 (0.5)	4 (2.2)	5 (1.4)	3 (1.9)	5 (1.2)
Any AE of Serious Immunologic Reaction	0 (0)	1 (0.6)	1 (0.3)	1 (0.6)	1 (0.2)
Any AE of Malignancies (including Lymphoma)	5 (2.7)	3 (1.7)	8 (2.2)	1 (0.6)	9 (2.1)

a – more than one AE possible per patient
N/A – not available
PY = total patient years of exposure and observation

7.1.5.5 Identifying common and drug-related adverse events

Event rates of AE categories do not indicate that receiving adalimumab treatment for an additional year increased the rate of AEs. No new adverse events by group categorization or by preferred term were identified.

7.1.6 Less Common Adverse Events

Less common but clinically significant adverse events are discussed in section 7.1.2 of this review. The study was too small in size to adequately discuss clinical significance of non-serious AEs that occurred in $\leq$ 1% of the subjects.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

General laboratory testing was performed according to the schedule outlined in section 7.1.5.1.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

N/A. This study was an open-label extension study where all subjects received adalimumab regardless of whether they received adalimumab or placebo in the original lead-in study. Thus, there is no concomitant control population in this study.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

N/A. Analyses based on measures of central tendency were not carried out because they would not be informative in this open-label study.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Results of laboratory testing were compared to normal values. Abnormal values were graded as grade 1, 2, 3, or 4 based on standardized toxicity scales. There was no pattern of laboratory abnormalities attributable to adalimumab administration noted in this study.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Patients with marked abnormal laboratories were examined and compared to normal values. Abnormal values were graded based on standardized toxicity scales. No pattern of dropout for laboratory abnormality was observed.

7.1.7.4 Additional analyses and explorations

N/A. Adalimumab is an approved product and its safety has previously been well characterized.

7.1.7.5 Special assessments

No special laboratory assessments were performed in this study.

7.1.8 Vital Signs

Vital signs were collected according to the schedule outlined in section 7.1.5.1. No pattern of abnormal vital signs was observed.

7.1.9 Electrocardiograms (ECGs)

ECGs were collected according to the schedule outlined in section 7.1.5.1. No pattern of ECG abnormalities was detected.

7.1.10 Immunogenicity

Information at the time of initial licensure of adalimumab indicated that approximately 1% of patients receiving concomitant methotrexate developed antibodies to adalimumab. Because of this low rate of anti-adalimumab antibody formation, further information on immunogenicity was not requested during Study DE019 OLE.

7.1.11 Human Carcinogenicity

Among 2468 rheumatoid arthritis patients with moderately to severely active disease treated with Humira® in clinical trials for a mean of 24 months (4870 patient-years of therapy), 10 lymphomas were observed for a rate of 0.21 cases per 100 patient-years. This is approximately 5-fold higher than expected in an age- and sex-matched general population based on the Surveillance, Epidemiology, and End Results Database. Other malignancies occurring in Study DE019 OLE are described in section 7.1.2.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no withdrawal phenomena and/or abuse potential issues identified with this product to date.

7.1.14 Human Reproduction and Pregnancy Data

A pregnancy registry has recently been established. No formal studies with adalimumab have been conducted in pregnant women.

7.1.15 Assessment of Effect on Growth

No data are available to adequately assess the product's effect on growth.

7.1.16 Overdose Experience

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. There are no known signs or symptoms of adverse reactions or effects resulting from overdosage.

7.1.17 Postmarketing Experience

The Office of Drug Safety identified 8 cases of cutaneous vasculitis that were reported to the Sponsor from spontaneous AE reports and recommended that this information be included in the package insert under the **Adverse Reaction Information from Spontaneous Reports** section.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The extent of exposure of subjects to adalimumab during Study DE019 OLE is presented in **Table 66**. Subjects received adalimumab for a mean of 344 days during the OLE study. The mean number of injections was 24. Subjects were exposed to a mean cumulative adalimumab dose of 959 mg.

Table 66: Extent of Exposure (Safety Set)

	Treatment Assignment During Study DE019			Study DE019 OLE
	20 mg weekly (N=165)	40 mg QOW (N=158)	Placebo (N=134)	40 mg EOW (N=457)
Duration of Treatment During Study DE019 OLE (days)				
N	165	158	134	457
Mean	337	351	343	344
Median	365	365	365	365
Range	15-392	85-392	16-382	15-392
Number of Injections				
N	165	158	133	457
Mean	24	25	24	24
Median	26	26	26	26
Range	1-26	6-26	1-26	1-26
Cumulative Dose of Adalimumab (mg)				
N	165	158	133	456
Mean	945	984	946	959
Median	1040	1040	1040	1040
Range	40-1040	40-1040	40-1040	40-1040

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

N/A. The Sponsor provided primary source data with data collected from studies under the Sponsor's IND. No secondary data sources were used.

7.2.3 Adequacy of Overall Clinical Experience

The Sponsor had an adequate number of moderately to severely active RA patients in the study. The current package insert for HUMIRA® indicates that 2468 RA subjects have participated in clinical trials with adalimumab for a median of 24 months. This experience indicates that a large

safety database already exists. No change in the target population with adalimumab is being proposed by this supplemental BLA. This patient population had pertinent risk factors to adequately assess the Sponsor's objectives of maintaining physical function and preventing structural damage due to RA.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new preclinical testing was performed with this approved product.

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing provided to subjects was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There was no in vitro or in vivo testing to assess drug-drug interaction.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No new potential AEs were identified and there are no new recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The Sponsor made no additional submissions and there was no new safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on the extensive prior experience, use of adalimumab is associated with a number of adverse events that appear drug related and these adverse events are fully described in the current package insert. No new adverse events were observed in Study DE019 OLE that are not already adequately described in the current package insert.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Sponsor met both primary efficacy endpoints in this study by providing data to support that adalimumab was able to maintain improved physical function and inhibit structural damage in active RA patients during two years of adalimumab treatment. Primary efficacy analyses, subgroup analyses, and secondary efficacy analyses (including quality of life assessments) were consistent with this conclusion. Overall, the safety profile in the open-label study was comparable to the lead-in study, with no increase in AE rates despite longer adalimumab administration.

9.2 Recommendation on Regulatory Action

Recommend approval of the efficacy supplement with revisions to the label.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management plan is required.

9.3.2 Required Phase 4 Commitments

The Sponsor is currently committed to providing periodic updates on new malignancy (including lymphoma) and serious infection (including tuberculosis and histoplasmosis) cases, and will continue to do so for 5 years post-approval. No new Phase 4 commitments are necessary.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

9.4 Labeling Review

The indication statement should be revised to add improvement in physical function. The clinical study section of the label should be revised to add the new information on improvement in physical function and inhibition of progression of structural damage over 2 years' treatment with adalimumab.

9.5 Comments to Applicant

There are no comments that would preclude the approval of the application during this review cycle.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

STATISTICAL REVIEW(S)

7/9/04

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

JUL 0 9 2004

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number: 125057.016
Drug Name: adalimumab (HUMIRA)
Indication(s): Improving physical function in patients with rheumatoid arthritis
Applicant: Abbott Lab.
Date(s): 10/07/03
Review Priority: Standard

Biometrics Division: Biologics Therapeutic Statistical Staff
Statistical Reviewer: Boguang Zhen
Concurring Reviewers: Aloka Chakravarty

Medical Division: DTBIMP
Clinical Team: Liang Li

Project Manager: Beverly Conner

Keywords: physical function, rheumatoid arthritis, adalimumab, HUMIRA, open-label study

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this 52-week open-label extension study, adalimumab treatment of 40 mg every other week in subjects with moderate to severe rheumatoid arthritis (RA) shows maintenance of improved physical function and sustained inhibition of radiographic structural damage during the second year of treatment. After an additional year of treatment with adalimumab, 82% (167 of 204) disability index of the heath assessment questionnaire (HAQ DI) 0.50 responders at Year 1 remained 0.50 responders at Year 2 (see Table 4) and a total of 54% (175 of 323) of subjects had no increase in TSS at Year 2 compared to Year 1 (see Table 8). Adalimumab treatment was generally safe and well tolerated.

As shown in the previous submission (BLA 125057.0) for the one-year double-blind study, patients treated with adalimumab demonstrated significant improvement in HAQ DI compared to placebo. Together with the first-year study findings, the efficacy results from this second year open-label study support the application of adding a new indication for improving physical function in patients with RA in the labeling.

1.2 Brief Overview of Clinical Studies

Abbott Laboratories submitted this BLA Supplement for their product -- adalimumab (HUMIRA). Adalimumab has been approved for the reduction of signs and symptoms and for inhibiting the progression of structural damage in patients with RA in December 2002. This supplement was submitted to the application for the approval of a new indication for improving physical function in patients with RA. Data and findings from Study DE019 were used to support the claim.

Study DE019 was a multicenter, double-blind, randomized, placebo-controlled, parallel group, Phase III study in which patients were assigned to one of two adalimumab dose groups (weekly dose of 20 mg adalimumab or 40 mg adalimumab every other week [eow]) or placebo for one year.

The 52-week open-label extension (OLE) study was a multicenter, open-label, continuation study involving subjects with RA receiving methotrexate (MTX) who were previously enrolled in Study DE019 and completed the double-blind placebo-controlled study period. All subjects in this period received adalimumab at 40 mg (total body dose) eow for 50 weeks (for a total treatment duration, including Study DE019, of 2 years). Each dose of study drug was self-administered by the subject as a single sc injection (0.8 mL). Administration of adalimumab was not blinded; however, the subjects' treatment randomization assignments in the blinded, lead-in study remained blinded until the Study DE019 database was locked.

Data and study report for the first year double-blind placebo-controlled period have been reviewed in the original submission. This review focuses only on data and results from the 52-week OLE study submitted in this supplement.

A total of 457 subjects were treated in Study DE019 OLE and a total of 415 (90.8% of 457) subjects completed Study DE019 OLE.

The primary endpoints for the open-label study are

1. **Maintenance of improved physical function for subjects originally receiving adalimumab in Study DE019.** Maintenance of improved physical function for subjects originally receiving adalimumab during the double-blind study period defined as the percentage of subjects treated with adalimumab during Study DE019 who achieved a 0.5 units or greater improvement in Week 52 disability index of the heath assessment questionnaire (HAQ DI), and then maintained an improvement of at least 0.5 units in HAQ DI at Week 104. Maintenance of improved physical function was demonstrated if 75% of HAQ DI 0.5 responder subjects (with lower confidence limit $\geq$ 60%) at Week 52 maintained responder status at Week 104. The criteria were set based on clinical judgment and agreed with by the clinical reviewers.

2. **Sustained inhibition of structural damage for subjects originally receiving adalimumab in Study DE019.** Sustained inhibition of structural damage defined as the change in structural damage, also called radiographic progression, and evaluated by changes in total Sharp score (TSS) during the second year of treatment compared to the Week 52. The Week 104 TSS change was derived by Week 104 TSS minus Week 52 TSS. The primary measure was the percentage of subjects with no change, defined as a change in TSS of less than or equal to zero during the second year of treatment with adalimumab. If $\geq$ 50% subjects observed a difference of $\leq$ 0 units in Week 104 TSS change (Week 104 TSS minus Week 52 TSS), or if the lower confidence limit of the observed percentage of subjects with no Week 104 TSS change is $\geq$ 37%, the two-year open-label TSS data demonstrate sustained inhibition of radiographic structural damage. The criteria were set based on clinical judgment and agreed with by the clinical reviewers.

The analysis for the first primary endpoint: Two hundred and four patients who received adalimumab during Study DE019 and were 0.50 responders at Week 52 were identified as the patient population for the analysis. A summary of the HAQ DI for 0.50 responders is presented in Table 1.

Table 1. Maintenance of Improved Physical Function (Week 52 HAQ DI 0.50 Responder Subset Subjects)

	Treatment Assignment in Study DE019		
	20 mg weekly n (%)	**40 mg eow n (%)**	**All Adalimumab n (%, 95% CI)**
0.50 HAQ DI responders at Week 52	109	95	204
0.50 responders at Week 104 (LOCF)	87 (79.8)	80 (84.2)	167 (**81.9**, 76.6 - 87.2)
0.50 responders at Week 104 (as observed)	76 (69.7)	76 (80.0)	152 (**74.5**, 68.5 - 80.5)

eow: every other week, LOCF: last observation carried forward

After an additional year of treatment with adalimumab, 81.9% (167 of 204) HAQ DI 0.50 responders remained 0.50 responders (95% CI: 76.6% - 87.2%) in the LOCF analysis. This result meets the pre-specified endpoint of having at least 75% of subjects who achieved a reduction in HAQ DI of 0.5 units at Week 52, maintained at least that improvement at Week 104, and had the lower limit of the CI above 60%. When treating patients who withdrew from the study prematurely as non-responders, the maintained HAQ DI 0.50 response rate is 74.5, a negligible difference from the pre-specified rate of 75%. Analyses on other secondary endpoints also support this finding.

The analysis for the second primary endpoint: The analysis includes 323 patients who received adalimumab during Study DE019 and then were entered into Study DE019 OLE, and who received at least one injection of 40 mg adalimumab during Study DE019 OLE. No change or decrease in the TSS score indicates a halting of the disease progression, whereas an increased score represents disease progression and/or joint worsening. At Week 104, a total of 54.2% (175 of 323) of subjects previously treated with adalimumab during Study DE019 had no increase in TSS (95% CI: 48.7% - 59.6%) compared to Week 52. This analysis includes 19 subjects who had no x-ray analysis in Study DE019 OLE. This result meets the pre-specified endpoint of having at least 50% of subjects without radiographic progression between Week 52 and Week 104 or having the lower limit of the CI for this percentage be at least 37%. Sensitivity analyses and analyses on other secondary endpoints also support this finding.

These efficacy findings show maintenance of improved physical function and sustained inhibition of radiographic structural damage during the second year of adalimumab treatment.

1.3 Statistical Issues and Findings

In this open-label continuation study, adalimumab treatment of 40 mg eow in subjects with moderate to severe RA who had inadequate response to MTX shows maintenance of improved physical function and sustained inhibition of radiographic structural damage. This reviewer has checked the sponsor's primary analyses and found that the results agree with what the sponsor has presented.

For the analysis of maintenance of improved physical function, the sponsor proposed imputing the missing values using LOCF method in the primary analysis. We expressed our concern on using this method and told the sponsor that this method may be OK as long as the percentage of missing data at Week 104 is not too high and the results were supported by the sensitivity analyses. When treating patients who withdrew from the study prematurely as non-responders, the maintained HAQ DI 0.50 response rate is 74.5, a negligible difference from the pre-specified rate of 75%, and the lower confidence limit > 60%. The pre-specified criteria for the claim were still met using this most conservative imputation method.

2. INTRODUCTION

2.1 Overview

Abbott Laboratories submitted this BLA Supplement for their product -- adalimumab (HUMIRA). Adalimumab has been approved for the reduction of signs and symptoms and for inhibiting the progression of structural damage in patients with RA in December 2002. This supplement was submitted to the application for the approval of a new indication for improving physical function in patients with RA. Data and findings from Study DE019 were used to support the claim.

RA is a common, chronic, inflammatory disorder of the joints predominantly affecting young adults and premenopausal women. A prevalence of 1% has been reported in diverse worldwide populations. The disease is characterized by a progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction.

Cytokines, hormone-like proteins that allow cells to communicate, play critical roles in normal biologic processes, such as cell growth, inflammation, and immunity. Two inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-1 (IL-1), are critical in the progression of inflammatory synovitis and articular matrix degradation, and, therefore represent promising targets for therapeutic intervention in RA. Clinical trials using agents that block TNF activity demonstrate the central role for this cytokine in the pathogenesis of RA and other autoimmune diseases. When TNF is inhibited, the levels of other pro-inflammatory cytokines are also reduced, such as IL-1 and interleukin-6 (IL-6). The most common strategies to neutralize TNF are through the administration of soluble TNF receptor molecules or monoclonal antibodies to TNF.

Adalimumab is the first human monoclonal antibody engineered by gene technology. It does not contain non-human or artificial protein sequences. Adalimumab binds only to TNF and has a half-life of approximately 2 weeks.

Study DE019 was a multicenter, double-blind, randomized, placebo-controlled, parallel group, Phase III study in which patients were assigned to one of two adalimumab dose groups (weekly dose of 20 mg adalimumab or 40 mg adalimumab every other week [eow]) or placebo. Adalimumab solution for injection and placebo were administered as a sc injection. This study was composed of three parts: 1) a washout period during which all previous DMARDs (except MTX) were discontinued. All patients were to be on a stable dose of MTX for at least 4 weeks prior to the screening visit; 2) a 52-week double-blind placebo controlled period; and 3) a 52-week open-label period. Adalimumab or placebo was administered as a single sc injection (1.6 mL/injection) weekly for up to 52 weeks during the double-blind placebo-controlled period.

The 52-week open-label extension (OLE) study was a multicenter, open-label, continuation study involving subjects with RA receiving MTX who were previously enrolled in Study DE019 and completed the double-blind placebo-controlled study period. All subjects in this period received adalimumab at 40 mg (total body dose) eow for 50 weeks (for a total treatment duration, including Study DE019, of 2 years). Each dose of study drug was self-administered by the subject as a single sc injection (0.8 mL). Administration of adalimumab was not blinded; however, the subjects' treatment randomization assignments in the blinded, lead-in study remained blinded until the Study DE019 database was locked.

Data and study report for the first year double-blind placebo-controlled period have been reviewed in the original submission. This review focuses only on data and results from the 52-week open-label extension (OLE) study submitted in this supplement.

2.2 Data Sources

The electronic data sets and study report for this BLA Supplement is located in 'EDR_PROD\2003 BLA\DCC# 133204' folder with the DCC tracking number: 133204.

This is a paperless BLA Supplement submission. All data were provided electronically and were installed in the Electronic Document Room (EDR) with a STN: 125057.16 and the Roadmap:

file://CBS5042329/M/EDR%20Submissions/2003%20BLA/DCC133204/roadmap.pdf

Data sources include all material reviewed, e.g. applicant study reports, data sets analyzed, and literature referenced.

This reviewer has no problem to access the study reports, locate and download the data sets.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study DE019 OLE was a multicenter, open-label, continuation study involving subjects with RA receiving MTX who were previously enrolled in and completed Study DE019, the double-blind placebo-controlled lead-in study. Subjects who participated in and completed Study DE019 were eligible to participate in Study DE019 OLE. Subjects who participated in Study DE019 were assigned to weekly placebo or one of two adalimumab

dose groups (20 mg adalimumab weekly or 40 mg adalimumab eow). All subjects in Study DE019 OLE received adalimumab at 40 mg eow for 50 weeks.

The primary objectives of this study are to evaluate the maintenance of improved physical function, sustained inhibition of structural damage, and long-term safety of eow sc doses of 40 mg adalimumab administered to subjects with RA receiving concurrent MTX therapy.

The primary efficacy endpoints are

1. **Maintenance of improved physical function for subjects originally receiving adalimumab in Study DE019.** Maintenance of improved physical function for subjects originally receiving adalimumab during the double-blind study period defined as the percentage of subjects treated with adalimumab during Study DE019 who achieved a 0.5 units or greater improvement in Week 52 disability index of the heath assessment questionnaire (HAQ DI), and then maintained an improvement of at least 0.5 units in HAQ DI at Week 104. Maintenance of improved physical function was demonstrated if 75% of HAQ DI 0.5 responder subjects (with lower confidence limit $\geq$ 60%) at Week 52 maintained responder status at Week 104. The criteria were set based on clinical judgment and agreed with by the clinical reviewers.

2. **Sustained inhibition of structural damage for subjects originally receiving adalimumab in Study DE019.** Sustained inhibition of structural damage defined as the change in structural damage, also called radiographic progression, and evaluated by changes in total Sharp score (TSS) during the second year of treatment compared to the Week 52. The Week 104 TSS change was derived by Week 104 TSS minus Week 52 TSS. The primary measure was the percentage of subjects with no change, defined as a change in TSS of less than or equal to zero during the second year of treatment with adalimumab. If $\geq$ 50% subjects observed a difference of $\leq$ 0 units in Week 104 TSS change (Week 104 TSS minus Week 52 TSS), or if the lower confidence limit of the observed percentage of subjects with no Week 104 TSS change is $\geq$ 37%, the two-year open-label TSS data demonstrate sustained inhibition of radiographic structural damage. The criteria were set based on clinical judgment and agreed with by the clinical reviewers.

No adjustment for multiplicity was carried out for the Study DE019 open-label analysis though there are two primary endpoints. As shown in the previous submission (BLA 125057.0) for the one-year double-blind study, patients treated with adalimumab demonstrated significant improvement in HAQ DI compared to placebo. Together with the first-year study finding, the HAQ DI primary endpoint in this second year open-label study was used to support the new indication of improving physical function. However, the TSS primary endpoint was not used to support a new indication, but to extend the claim for the inhibition of progression of structural damage from one year to two year.

Most of the analyses were done descriptively, and the confirmatory analysis was based on the comparison between the results from the descriptive statistics and the predefined

clinical objectives. Statistical summary tables were displayed by randomized treatment groups (*i.e.*, 20 mg weekly, 40 mg eow, and placebo) and open-label dose (40 mg eow). Two approaches were used: (a) data as observed and (b) data as imputed (LOCF).

For the HAQ primary endpoint analysis (maintenance of improved physical function), the LOCF method for imputing the missing values was used in the primary analysis. Sensitivity analysis was performed on Week 52 HAQ DI 0.5 responder subset subjects to explore the possibility of introduced bias. The percentage of HAQ DI 0.5 responder subjects at Week 52 maintained responder status at Week 104 was re-assessed by treating missing values as non-responder.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

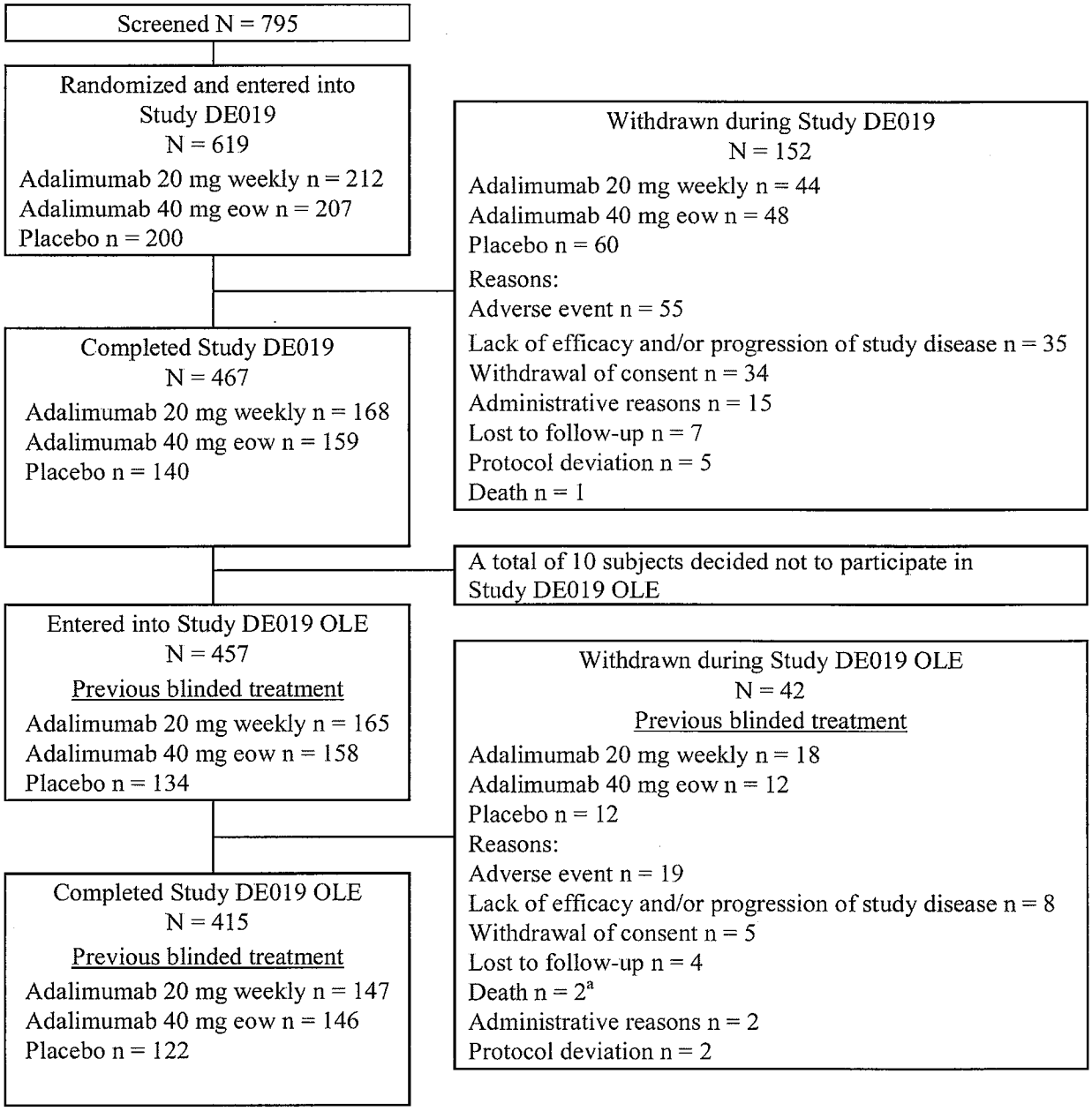
The disposition of subjects who entered Study DE019 OLE is summarized in Figure 1. A total of 457 subjects were treated in Study DE019 OLE. The subjects were entered across 83 sites, and the number of subjects entered per site ranged from one (Site Numbers 15, 30, 51, 54, 68, 83, and 100) to 18 (Site Number 24). A total of 415 (90.8% of 457) subjects completed Study DE019 OLE, and a total of 42 (9.2% of 457) subjects were prematurely withdrawn from Study DE019 OLE. Of these, 19 subjects withdrew due to an AE; 8 subjects withdrew due to lack of efficacy and/or progression of study disease; 5 subjects withdrew due to withdrawal of consent; 4 subjects were lost to follow-up; 2 subjects died; 2 subjects withdrew due to administrative reasons; and 2 subjects withdrew due to protocol deviations. A third subject died 2 days after withdrawing from the study, the reason for withdrawal from the study was due to an AE.

The full analysis set (N=323) was the primary analysis population. It consisted of all subjects who received adalimumab during Study DE019 and then were entered into Study DE019 OLE, and who received at least one injection of 40 mg adalimumab during Study DE019 OLE.

A summary of demographic characteristics for the 323 subjects treated with adalimumab during Study DE019 who later enrolled into Study DEO19 OLE, and all subjects who enrolled in Study DE019 OLE is presented in Table 2. Minimal changes were observed between the demographics of the 323 subjects at entry into Study DE019 who received adalimumab and later enrolled into Study DE019 OLE. At entry into Study DE019 OLE (*i.e.*, Week 54), subjects ranged in age from 22 to 88 years. There were more female (340 [74.4%] of 457) than male (117 [25.6%] of 457) subjects. The majority of subjects (391 [85.6%] of 457) were Caucasian; Hispanic, Black, Asian, and Other races comprised the remaining 66 (14.4%) of 457 subjects. The median body weight for all subjects was 78.7 kg (range: 41.4 to 154.5 kg), and the median height was 165.8 cm (range: 132 to 191 cm).

A summary of disease characteristics for the 323 subjects treated with adalimumab during Study DE019 who later enrolled into Study DEO19 OLE, and all subjects who enrolled in Study DE019 OLE is presented Table 3. Minimal changes were observed between the disease characteristics of the 323 subjects at entry into Study DE019 who received adalimumab and later enrolled into Study DE019 OLE.

Figure 1. Subject Disposition



a A third subject died 2 days after withdrawing due to an AE and is listed as being withdrawn due to that AE.

Table 2. Demographic Characteristics (All Treated Subjects)

Demographic Characteristic	Entry into Study DE019 Subjects Previously Treated with Adalimumab (N = 323)[a]	Baseline (Week 0) Data for Subjects Enter Study DE019 OLE (N = 457)
Age (years)		
Mean ± SD	57.8 ± 12.1	57.3 ± 12.0
Median	58	58
(range)	(22-88)	(22- 88)
Age group n (%)		
< 40	26 (8.0)	36 (7.9)
40 - 64	197 (61.0)	289 (63.2)
65 - 74	77 (23.8)	103 (22.5)
≥ 75	23 (7.1)	29 (6.3)
Sex n (%)		
Female	245 (75.9)	340 (74.4)
Male	78 (24.1)	117 (25.6)
Ethnic origin n (%)		
Caucasian	278 (86.1)	391 (85.6)
Black	20 (6.2)	28 (6.1)
Hispanic	15 (4.6)	24 (5.3)
Asian	6 (1.9)	8 (1.8)
Other	4 (1.2)	6 (1.3)
Body weight (kg)		
Mean ± SD	78.1 ± 18.8	78.7 ± 19.5
Median	76	76
(range)	(41-153)	(41 -155)
Body weight category (kg)		
< 60	61 (18.9)	79 (17.3)
> 60-70	62 (19.2)	95 (20.8)
> 70-85	100 (31.0)	138 (30.2)
> 85	100 (31.0)	145 (31.7)
Height (1cm)[b]		
Mean ± SD	165.3 ± 10.3	165.8 ± 10.1
Median	165	165
(range)	(132-191)	(132 -191)

a Subjects who entered study DE019 OLE who were randomized to adalimumab during study DE019.

b One patient did not have a height recorded.

SD: standard deviation

Table 3. Disease Characteristics (All Treated Subjects)

Demographic Characteristic	Entry into Study DE019 Subjects Previously Treated with Adalimumab (N = 323)[a]	Baseline (Week 0) Data for Subjects Entering Study DE019 OLE (N = 457)
Duration of RA (years)		
N	322	456
Mean ± SD	11.1 ± 9.1	10.9 ± 8.9
Median	8.4	8.2
(range)	(0.2 - 52.1)	(0.2 - 52.1)
Duration of Morning Stiffness (min)		
N	319	451
Mean ± SD	103.1 ± 145.1	103.2 ± 140.3
Median	60.0	60.0
(range)	(0.0 - 1440.0)	(0.0 - 1440.0)
TJC (0-68 joints)		
N	323	457
Mean ± SD	27.7 ± 12.9	28.1 ± 13.3
Median	25.0	26.0
(range)	(9.0 - 66.0)	(9.0 - 68.0)
SJC (0-66 joints)		
N	323	457
Mean ± SD	19.5 ± 9.6	19.3 ± 9.5
Median	18.0	17.0
(range)	(6.0 - 55.0)	(6.0 - 57.0)
Patient Assessment of Pain (100 mm VAS)		
N	323	457
Mean ± SD	55.8 ± 21.7	55.4 ± 21.9
Median	58.0	58.0
(range)	(5.0 - 98.0)	(5.0 - 100.0)
Patient Global Assessment of Disease Activity (100 mm VAS)		
N	323	457
Mean ± SD	52.8 ± 21.9	52.7 ± 21.8
Median	52.0	52.0
(range)	(1.0 - 99.0)	(1.0 - 100.0)
Physician Global Assessment of Disease Activity (100 mm VAS)		
N	323	457
Mean ± SD	61.8 ± 16.6	61.4 ± 16.6
Median	64.0	63.0
(range)	(4.0 - 99.0)	(4.0 - 100.0)
CRP (mg/dL)		
N	323	457
Mean ± SD	1.7 ± 2.0	1.6 ± 1.9
Median	1.0	1.0
(range)	(0.4 - 16.1)	(0.4 - 16.1)
HAQ DI		
N	323	456
Mean ± SD	1.4 ± 0.6	1.4 ± 0.6
Median	1.5	1.5
(range)	(0.0 - 2.8)	(0.0 - 2.9)

a Subjects who entered study DE019 OLE who were randomized to adalimumab during study DE019.

3.1.3 The HAQ DI Results

One of the two primary efficacy endpoints was maintenance of improved physical function. Maintenance of improved physical function was assessed using subjects treated with adalimumab during Study DE019 who were 0.50 responders at Week 52 and who were followed to Week 104 to determine whether they maintained an important clinical improvement in baseline HAQ DI score of 0.5 units or greater. Two hundred and four patients who received adalimumab during Study DE019 and were 0.50 responders at Week 52 were identified as the patient population for this analysis. A summary of the HAQ DI for 0.50 responders is presented in Table 4.

Table 4. Maintenance of Improved Physical Function (Week 52 HAQ DI 0.50 Responder Subset Subjects)

	Treatment Assignment in Study DE019		
	20 mg weekly n (%)	**40 mg eow n (%)**	**All Adalimumab n (%, 95% CI)**
0.50 HAQ DI responders at Week 52	109	95	204
0.50 responders at Week 104 (LOCF)	87 (79.8)	80 (84.2)	167 (**81.9**, 76.6 - 87.2)
0.50 responders at Week 104 (as observed)	76 (69.7)	76 (80.0)	152 (**74.5**, 68.5 - 80.5)

eow: every other week, LOCF: last observation carried forward

After an additional year of treatment with adalimumab, 81.9% (167 of 204) HAQ DI 0.50 responders remained 0.50 responders (95% CI: 76.6% - 87.2%) in the LOCF analysis. This result meets the pre-specified endpoint of having at least 75% of subjects who achieved a reduction in HAQ DI of 0.5 units at Week 52, maintained at least that improvement at Week 104, and had the lower limit of the CI above 60%. When treating patients who withdrew from the study prematurely as non-responders, the maintained HAQ DI 0.50 response rate is 74.5, a negligible difference from the pre-specified rate of 75%.

To test the robustness of the primary efficacy endpoint, a secondary analysis was done on the following settings:

Maintenance of improved physical function assessed by HAQ DI was evaluated in subjects treated with adalimumab during Study DE019 who were 0.22, 0.75, or 1.0 responders at Week 52 and who were followed through Week 104 to determine whether they maintained or improved upon their respective response levels. A summary of the maintenance of the HAQ DI is presented for all treated subjects in Table 5. The majority of the subjects treated with adalimumab during Study DE019 maintained the improved physical function during the second year of treatment using different definitions of responders.

Table 5. Maintenance of the HAQ DI for 0.22, 0.75, and 1.0 Responders (Week 52 HAQ DI 0.22, 0.75, or 1.0 Responder Subset Subjects)

HAQ DI Responder Levels		Treatment Assignment in Study DE019					
		20 mg weekly n (%)		40 mg eow n (%)		All Adalimumab n (%)	
0.22 Responders	Week 52	134		124		258	
	Week 104	105	**(78.4)**	109	**(87.9)**	214	**(82.9)**
0.75 Responders	Week 52	78		71		149	
	Week 104	57	**(73.1)**	57	**(80.3)**	114	**(76.5)**
1.0 Responders	Week 52	55		48		103	
	Week 104	33	**(60.0)**	28	**(58.3)**	61	**(59.2)**

As observed data is presented
eow: every other week

The number of subjects who achieved the HAQ DI 0.22, 0.50, 0.75, or 1.0 response levels was determined at Week 54 (entry for Study DE019 OLE) and Week 104. A summary of the HAQ DI is presented for all treated subjects in Table 6. Mean HAQ DI scores are presented for all treated subjects in Table 7. Following two years of treatment with adalimumab, large proportions of subjects had responses at the HAQ DI levels of 0.22, 0.50, 0.75, and 1.0. Analysis of mean changes in the HAQ DI in adalimumab-treated subjects showed the improvement in physical functioning achieved at Week 54 was similar at Week 104, thereby supporting the primary efficacy analysis.

Table 6. Number of Responders in the HAQ DI Levels of 0.22, 0.50, 0.75, and 1.0 (All Treated Subjects)

HAQ DI Responder Level		Treatment Assignment in Study DE019					
		20 mg weekly (N = 165) n (%)		40 mg eow (N = 158) n (%)		All Adalimumab (N = 323) n (%)	
0.22 responders	Week 54[a]	132	(80.0)	129	(81.6)	261	(80.8)
	Week 104	112	(67.9)	117	(74.1)	229	**(70.9)**
0.50 responders	Week 54[a]	104	(63.0)	95	(60.1)	199	(61.6)
	Week 104	91	(55.2)	88	(55.7)	179	**(55.4)**
0.75 responders	Week 54[a]	78	(47.3)	72	(45.6)	150	(46.4)
	Week 104	67	(40.6)	68	(43.0)	135	**(41.8)**
1.0 responders	Week 54[a]	52	(31.5)	49	(31.0)	101	(31.3)
	Week 104	40	(24.2)	38	(24.1)	78	**(24.1)**

a Week 54 is entry visit for Study DE019 OLE
As observed data is presented
eow: every other week

Table 7. Mean HAQ DI Scores (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg eow (N = 158)		All Adalimumab (N = 323)	
HAQ DI Score	N	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Week 0	165	1.44 ± 0.64	158	1.43 ± 0.63	323	1.44 ± 0.63
Week 54[a]	161	0.76 ± 0.71	157	0.76 ± 0.66	318	0.76 ± 0.68
Week 104	146	0.79 ± 0.71	146	0.74 ± 0.65	292	0.76 ± 0.68

a Week 54 is entry visit for Study DE019 OLE

As observed data is presented

eow: every other week, SD: standard deviation

Therefore, the results are consistent with a conclusion of maintenance of improved physical function following two years of treatment with adalimumab.

3.1.4 The TSS Results

The other co-primary efficacy endpoint was sustained inhibition of structural damage. Sustained inhibition of structural damage as measured by the TSS, the objective measure of inhibition of progression of structural damage, was categorized by response (no change or decreased score versus increased score) between Week 52 and Week 104 and is presented in Table 8. No change in the TSS indicates a halting of the disease progression, whereas an increased score represents disease progression and/or joint worsening.

Table 8. Sustained Inhibition of Structural Damage as Measured by the change in TSS between Week 52 and Week 104 (All Treated Subjects)

	Treatment Assignment in Study DE019		
Total Sharp Score	20 mg weekly (N = 165) n (%)	40 mg eow (N = 158) n (%)	All Adalimumab (N = 323) n (%, 95% CI)
Subjects with no change or decreased score	87 (52.7)	88 (55.7)	175 (**54.2**, 48.7-59.6)
Subjects with increased score	65 (39.4)	64 (40.5)	129 (39.9, 34.6-45.3)
Missing	13 (7.9)	6 (3.8)	19 (5.9, 3.3-8.4)

eow: every other week

At Week 104, a total of 54.2% (175 of 323) of subjects previously treated with adalimumab during Study DE019 had no increase in TSS (95% CI: 48.7% - 59.6%) compared to Week 52. If compared to the baseline (Week 0), 54.8% (177 of 323) of subjects had no increase in TSS. These analyses include 19 subjects who had no x-ray analysis in Study DE019 OLE. The results meet the pre-specified endpoint of having at

least 50% of subjects without radiographic progression between Week 52 and Week 104 or having the lower limit of the CI for this percentage be at least 37%.

Analysis using only the 304 subjects who had x-rays available during Study DE019 OLE, and even higher percentage (57.6%, 175 of 304) had no radiographic progression.

To test the robustness of all primary efficacy endpoints, a secondary analysis was done on the following settings.

A summary of the change and percent change of mean TSS from Study DE019 entry and Study DE019 OLE entry is presented in Table 9. An increase in the TSS is indicative of disease progression and/or joint worsening. In contrast, no change in TSS represents a halting of the disease progression, and a decrease represents improvement. The changes in TSS following two years of treatment with adalimumab are reflective of sustained inhibition of structural damage as assessed by the radiographic evaluation.

Table 9. TSS (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		**40 mg eow (N = 158)**		**All Adalimumab (N = 323)**	
Total Sharp Score	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Mean change from Week 0 to Week 52	152	-0.1 ± 5.7	153	-0.7 ± 7.1	305	**-0.4** ± 6.5
Mean change from Week 52 to Week 104	152	1.0 ± 8.2	152	0.6 ± 8.9	304	**0.8** ± 8.6

As observed data is presented

eow: every other week, SD: standard deviation

Sustained inhibition of structural damage as measured by a change of less than or equal to 0.5 in the TSS, the objective measure of inhibition of progression of structural damage, was categorized by response between Week 52 and Week 104 and is presented in Table 10. Sixty-five percent (65%) (N = 212, 95% CI: 60.5% - 70.8%) of the 323 subjects treated with adalimumab during Study DE019 had an increase of 0.5 or less in TSS compared to Week 52.

Therefore, these results are consistent with the conclusion of sustained inhibition of radiographic progression following two years of treatment with adalimumab.

Table 10. Sustained Inhibition of Structural Damage as Measured by the 0.5 Level of the TSS (All Treated Subjects)

	Treatment Assignment in Study DE019		
Total Sharp Score 0.5 Level	**20 mg weekly (N = 165) n (%)**	**40 mg eow (N = 158) n (%)**	**All Adalimumab (N = 323) n (%, 95% CI)**
Change in TSS of ≤ 0.5	109 (66.1)	103 (65.2)	212 (**65.6**, 60.5-70.8)
Change in TSS of > 0.5	43 (26.1)	49 (31.0)	92 (**28.5**, 23.6-33.4)
Missing	13 (7.9)	6 (3.8)	19 (5.9, 3.3-8.4)

As observed data is presented
eow: every other week

3.1.5 Other Important Efficacy Results

ACR20, ACR50, and ACR70 Responses: The percentage of subjects previously treated with adalimumab meeting ACR20 criteria was **66.9%** (216 of 323 subjects) at Week 54 and **61.9%** (200 of 323 subjects) at Week 104. The percentage of subjects previously treated with adalimumab meeting ACR50 criteria was **49.8%** (161 of 323 subjects) at Week 54 and **44.0%** (142 of 323 subjects) at Week 104. The percentage of subjects previously treated with adalimumab meeting ACR70 criteria was **26.3%** (85 of 323 subjects) at Week 54 and **28.5%** (92 of 323 subjects) at Week 104.

Major Clinical Response: The major clinical response is defined as an ACR70 response over a 6-month period during Study DE019 or Study DE019 OLE. The percentage of subjects previously treated with adalimumab with a major clinical response during Study DE019 or Study DE019 OLE was **24%** (79 of 323 subjects) at Week 104. If all randomized patients were included in the analysis, the major clinical response rate was 19% (79 of 419) at Week 104.

SF-36 Questionnaire: Mean SF-36 questionnaire domain scores are presented for all treated subjects in Table 11. Increases in SF-36 scores indicate improvement and decreases represent worsening of the disease. Clinically meaningful improvements were defined in all domains as a > 5 point increase while clinically meaningful improvements in the summary component scores were defined as > 2.5 point increase. There was a substantial improvement (*i.e.*, increased SF-36 scores) during Study DE019 for those subjects treated with adalimumab. At Week 104, subjects previously treated with adalimumab maintained stable SF-36 domain scores compared to Week 52.

Table 11. SF-36 Questionnaire Domain Scores (All Treated Subjects)

	Treatment Assignment in Study DE019					
	20 mg weekly (N = 165)		40 mg eow (N = 158)		All Adalimumab (N = 323)	
SF-36 Parameter	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Physical Function						
Week 0	165	38.7 ± 23.1	157	40.3 ± 22.8	322	39.4 ± 22.9
Week 52	165	57.1 ± 26.5	158	57.4 ± 26.7	323	57.2 ± 26.5
Week 104	165	56.7 ± 26.2	158	58.1 ± 28.7	323	57.4 ± 27.4
Role Physical						
Week 0	165	23.5 ± 34.8	158	25.8 ± 36.4	323	24.6 ± 35.5
Week 52	165	59.0 ± 38.7	158	52.4 ± 42.6	323	55.8 ± 40.7
Week 104	165	55.2 ± 43.1	158	53.5 ± 43.3	323	54.3 ± 43.1
Bodily Pain						
Week 0	165	38.4 ± 17.2	158	37.8 ± 16.3	323	38.1 ± 16.7
Week 52	165	62.9 ± 21.3	158	63.2 ± 21.7	323	63.0 ± 21.5
Week 104	165	61.1 ± 23.1	158	62.0 ± 23.7	323	61.5 ± 23.4
General Health						
Week 0	164	50.8 ± 21.2	158	51.4 ± 19.7	322	51.1 ± 20.4
Week 52	165	63.8 ± 20.2	158	63.6 ± 20.4	323	63.7 ± 20.3
Week 104	165	62.5 ± 20.8	158	63.4 ± 21.7	323	62.9 ± 21.2
Vitality						
Week 0	164	38.0 ± 19.5	158	36.4 ± 20.8	322	37.2 ± 20.1
Week 52	165	55.5 ± 22.0	158	55.4 ± 24.1	323	55.5 ± 23.0
Week 104	165	54.8 ± 23.4	158	55.0 ± 24.2	323	54.9 ± 23.8
Social Functioning						
Week 0	165	65.2 ± 26.1	158	64.6 ± 26.6	323	64.9 ± 26.3
Week 52	165	81.4 ± 20.6	158	78.1 ± 23.0	323	79.8 ± 21.9
Week 104	165	78.2 ± 21.5	158	77.1 ± 26.7	323	77.6 ± 24.2
Role Emotional						
Week 0	165	57.8 ± 44.7	158	60.1 ± 42.1	323	58.9 ± 43.4
Week 52	165	80.0 ± 34.7	158	73.2 ± 37.9	323	76.7 ± 36.4
Week 104	165	73.9 ± 38.6	158	73.0 ± 37.8	323	73.5 ± 38.2
Mental Health						
Week 0	164	70.8 ± 18.7	158	70.1 ± 18.6	322	70.4 ± 18.7
Week 52	165	77.6 ± 17.7	158	77.3 ± 17.6	323	77.4 ± 17.7
Week 104	165	77.0 ± 16.6	158	77.8 ± 18.6	323	77.4 ± 17.6
Physical Component Summary						
Week 0	164	29.4 ± 9.0	157	29.9 ± 8.2	321	29.6 ± 8.6
Week 52	165	39.5 ± 10.6	158	39.3 ± 10.8	323	39.4 ± 10.7
Week 104	165	39.2 ± 10.6	158	39.5 ± 11.3	323	39.3 ± 11.0
Mental Component Summary						
Week 0	164	49.5 ± 12.0	157	49.0 ± 11.3	321	49.3 ± 11.6
Week 52	165	53.8 ± 10.2	158	52.6 ± 10.2	323	53.2 ± 10.2
Week 104	165	52.7 ± 9.6	158	52.5 ± 10.4	323	52.6 ± 10.0

LOCF data is presented.

eow: every other week, LOCF: last observation carried forward, SD: standard deviation

3.2 Evaluation of Safety

All safety assessments were performed to evaluate the primary objective of long-term safety and secondary objective of tolerability of eow sc doses of 40 mg adalimumab. A total of 457 subjects received adalimumab at a dose of 40 mg sc eow in the study. Of these 457 subjects, 165 had received adalimumab 20 mg sc weekly, 158 had received adalimumab 40 mg sc eow, and 134 had received placebo sc eow during the double-blind period of the lead-in study, Study DE019.

In summary, the overall AE profile associated with adalimumab treatment was comparable during the first year of double-blind treatment in Study DE019 and the second year of open-label treatment during the extension study (Study DE019 OLE). The percent of subjects who experienced a treatment-emergent SAE during the double-blind phase (14.3% of 419 subjects) was comparable to the percent subjects who experienced a treatment-emergent SAE during Study DE019 OLE (14.9% of 457 subjects). Serious infectious events occurred in similar proportions of subjects (3.8% vs. 3.7% subjects) treated with adalimumab in the double-blind and open-label periods, respectively. The frequency of malignancies was (2.0% of 457 subjects) during Study DE019 OLE. The frequency of malignancies in Study DE019 OLE was similar to the frequency of malignancies in Study DE019 (1.9% of 419 subjects).

More detailed evaluation of safety can be seen in the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The sponsor has performed analysis in subgroup populations using Mean HAQ DI scores. The subgroup analyses were performed on all treated subjects and were based on Study DE019 entry data for sex (male or female), age (< 65 or ≥ 65), race (Caucasian, Black, Asian, Hispanic, or Other), body weight (≤ 70 kg or > 70 kg), corticosteroid use (yes or no), RF status (positive or negative), and duration of RA (0-2, 2-5, 5-10, or > 10 years). Subgroup analyses showed no clinically relevant differences in the level of improved physical function achieved.

4.2 Other Special/Subgroup Populations

A total of 457 subjects were treated in Study DE019 OLE. The subjects were entered across 83 sites in the US and Canada, and the number of subjects entered per site ranged from one (Site Numbers 15, 30, 51, 54, 68, 83, and 100) to 18 (Site Number 24).

For the analysis of maintenance of improved physical function (the primary endpoint for supporting the new indication), 204 patients who achieved a 0.5 units or greater improvement in Week 52 HAQ DI were identified as the analysis data set. Among this group of patients, the number of patients entered per site ranged from zero to 7. The number of patients per site was too small to conduct a meaningful analysis by site.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In this open-label continuation study, adalimumab treatment of 40 mg eow in subjects with moderate to severe RA who had inadequate response to MTX shows maintenance of improved physical function and sustained inhibition of radiographic structural damage. This reviewer has checked the sponsor's primary analyses and found that the results agree with what the sponsor has presented.

For the analysis of maintenance of improved physical function, the sponsor proposed imputing the missing values using LOCF method in the primary analysis. We expressed our concern on using this method and told the sponsor that this method may be OK as long as the percentage of missing data at Week 104 is not too high and the results were supported by the sensitivity analyses. When treating patients who withdrew from the study prematurely as non-responders, the maintained HAQ DI 0.50 response rate is 74.5, a negligible difference from the pre-specified rate of 75%, and the lower confidence limit > 60%. The pre-specified criteria for the claim were still met using this most conservative imputation method.

5.2 Conclusions and Recommendations

In this 52-week open-label extension study, adalimumab treatment of 40 mg every other week in subjects with moderate to severe RA shows maintenance of improved physical function and sustained inhibition of radiographic structural damage during the second year of treatment. After an additional year of treatment with adalimumab, 82% (167 of 204) HAQ DI 0.50 responders at Year 1 remained 0.50 responders at Year 2 (see Table 4) and a total of 54% (175 of 323) of subjects had no increase in TSS at Year 2 compared to Year 1 (see Table 8). Adalimumab treatment was generally safe and well tolerated.

As shown in the previous submission (BLA 125057.0) for the one-year double-blind study, patients treated with adalimumab demonstrated significant improvement in HAQ DI compared to placebo. Together with the first-year study findings, the efficacy results from this second year open-label study support the application of adding a new indication for improving physical function in patients with RA in the labeling.

SIGNATURES/DISTRIBUTION LIST PAGE

Boguang Zhen

Boguang Zhen, Ph.D.
Primary Statistical Reviewer/Team Leader

7/9/04
Date

Concur:

Aloka Chakravarty

Aloka Chakravarty, Ph.D.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

OTHER REVIEW(S)

MEMORANDUM

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

DATE: July 21, 2004

FROM: Gerard G. Nahum, MD
Pregnancy Labeling Team, OND, HFD-020

THROUGH: Sandra Kweder, MD
Deputy Director, OND, HFD-020

TO: Earl S. Dye
HHS/ FDA/ CDER/ OND/ ODE VI/ DRMP
HFM-585, WOC II 6047

SUBJECT: Adalimumab, STN 125057/16 efficacy supplement – additional information concerning pregnancy registry

Consult received: July 8, 2004
Due date: July 30, 2004

I. EXECUTIVE SUMMARY

Adalimumab (HUMIRA®) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor. An efficacy supplement for this product is currently under review. The pregnancy labeling team has been consulted to provide input on labeling – specifically whether a statement should be inserted into the supplementary Patient Information leaflet to inform female readers that if they either are or become pregnant while using HUMIRA®, that a pregnancy registry exists and that they should consider speaking to their healthcare provider(s) about enrollment. In addition to the information provided in the standard Package Insert concerning the existence of a pregnancy registry and the toll free contact number, the pregnancy labeling team provides the recommendation that the following wording should be incorporated into the Patient Information leaflet:

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 healthcare 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 this medication, you may wish to participate in a pregnancy registry to gather additional information about the use of this medication during pregnancy by calling the following toll free number: 1-877-311-8972.

II. BACKGROUND

Adalimumab (HUMIRA®) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor. The current approved labeling contains the following statement at the end of the pregnancy section:

"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."

An efficacy supplement for this product is currently under review. The pregnancy labeling team has been consulted to determine whether a statement should be inserted into the supplementary Patient Information leaflet to inform female readers that if they either are or become pregnant while using HUMIRA®, that a pregnancy registry exists and that they should consider speaking to their healthcare provider(s) about enrolling.

III. LITERATURE REVIEWED

The proposed label for HUMIRA® dated July 2, 2004, the proposed Patient Information leaflet dated July 2, 2004, and the letter to Beverly Conner, Pharm. D. from James Steck of Regulatory Affairs from Abbott Laboratories dated July 2, 2004 have been reviewed.

IV. RECOMMENDATION/ CONCLUSIONS

It is the recommendation of the pregnancy labeling team that the wording listed in section I above should be incorporated into the supplementary Patient Information leaflet for HUMIRA®. In addition, it is the general recommendation of the pregnancy labeling team that when a pregnancy registry exists and there is a supplementary Patient Information leaflet for a drug or biologic, that a brief statement concerning the existence, purpose, and contact information of the pregnancy registry be incorporated in the Patient Information leaflet, as well as in the standard Package Insert.

Gerard G. Nahum, MD
Medical Officer

Concurrence by:

Kathleen Uhl, MD
Medical Team Leader

Copies:
HFD-020 Kweder, Uhl, Kennedy
HFM-588 Conner

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

PID#: D030673

DATE: July 13, 2004

FROM: Hyon J. Kwon, Pharm.D., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430 Mark Avigan 7/13/04

TO: Marc Walton, M.D., Ph.D., Director
Division of Therapeutic Biological Internal Medicine, HFM-576

SUBJECT: One-year postmarketing safety review of adalimumab (Humira®, BLA NO. STN 125057/16)

1. EXECUTIVE SUMMARY/INTRODUCTION

This consult is in response to a request made by the Division of Therapeutic Biological Internal Medicine (DTBIM) to review all postmarketing adverse events reported with the use of adalimumab (Humira®) since its approval on 12/31/02, with a focus on any serious, unlabeled adverse events. Abbott Laboratories has recently submitted a 10-month efficacy supplement to include improved physical function and quality of life information in its package insert and PPI.[1]

As of March 5, 2004, 1121 adverse event reports linked to adalimumab were in the AERS database. The three most commonly reported adverse event terms were injection site burning, injection site erythema, and injection site pain, which are already well known, labeled events. Of 1121 reports, 305 (27%) reports were serious and 67 cases reported death as an outcome. The sixty-seven death cases were further reviewed; four cases were duplicates. Deaths in 22 cases were related to an infectious etiology. In the remaining 41 cases, the cause of death appeared to be secondary to the underlying disease, unrelated to the drug, or contained insufficient information.

The reported adverse event terms from these 1121 cases were reviewed by the DTBIM medical officer.[2] He has requested a more in-depth review of adult respiratory distress syndrome (ARDS) and interstitial lung disease (ILD) cases to determine whether these were disease-related or drug-related. One of each of the following pulmonary events unrelated to other etiology were identified; 1) ARDS, 2) interstitial pneumonitis, 3) lymphocytic alveolitis, 4) unspecified

inflammatory process of lungs, and 5) unspecified respiratory problem resulting in death. All patients were concomitantly receiving methotrexate (MTX), an agent that has been well associated with lung injury. In the interstitial pneumonitis case, MTX was initiated at the same time as adalimumab. Only the interstitial pneumonitis case reported resolution with therapy. Two deaths were reported; ARDS and one death due to unspecified respiratory problem. The lymphocytic alveolitis event did not resolve at the last follow-up and the outcome of the unspecified inflammatory process of lung was unknown.

Literature reports[3] have recently raised concerns about possible hepatic injury with similar anti-rheumatic products. Thus, hepatic/hepatobiliary events were also reviewed. Five cases of notable hepatic/hepatobiliary events were found: four cases of increased liver enzymes such as AST, ALT and/or alkaline phosphatase (1 reported development of autoimmune hepatitis with cirrhosis) and one case of primary biliary cirrhosis (PBC). One death was reported in a patient with ALT elevation; the cause of death was unknown and appeared unrelated to the hepatic event. The PBC case improved with ursodiol therapy and the outcome was unknown in the other two cases.

Lastly, renal events were reviewed prompted by one literature case report of nephrotic syndrome associated with the use of adalimumab.[4] However, only two cases of renal failure were identified and both had risk factors/confounders. The renal failure event abated after drug discontinuation in one patient whereas it had not yet resolved in the other patient.

In summary, all the adverse events including deaths that were reported during the first year since the marketing of adalimumab were examined. In addition, pulmonary events (specifically ARDS and ILD), hepatic/ hepatobiliary events, and renal events reported with adalimumab therapy were reviewed in-depth. Our review did not find any serious, unlabeled adverse events and the current label seems to appropriately reflect the postmarketing events to date. We will continue to closely monitor incoming adverse event reports.

2. DRUG INFORMATION/LABELING[5]

Adalimumab (Humira®) was approved for marketing in US on 12/31/02 for the treatment of rheumatoid arthritis (RA) unresponsive to one or more Disease Modifying Anti-rheumatic Drugs (DMARDs). Adalimumab is a human monoclonal antibody that binds and thus blocks the activity of tumor necrosis factor-alpha.

The current label has a black box warning for the risk of infections, and warnings/precautions for serious infections/tuberculosis, neurologic events, malignancies/immunosuppression, general (allergic reactions), and autoimmunity (lupus-like syndrome).

Renal events are currently not labeled, but the following pulmonary and hepatic terms are listed under Other Adverse Event 'occurring at an incidence of less than 5% in patients treated with HUMIRA':

> Digestive System:.... hepatic necrosis ...

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

3. MEDICAL LITERATURE SUMMARY

A medical literature search in PubMed resulted in one adverse event report of nephrotic syndrome related to the use of adalimumab. Broeder[4] described a patient who developed nephrotic syndrome while receiving adalimumab for the treatment of RA. The patient experienced proteinuria which disappeared upon discontinuation of adalimumab and reappeared upon re-administration. The patient also had a renal biopsy that showed membranous glomerulopathy.

4. SUMMARY OF ALL CASES

On March 5, 2004, the AERS database was searched to capture all adverse events reported with adalimumab therapy. The search resulted in 1121 reports.

Of 1121 reports, 305 (27%) reports were serious and 67 cases reported death as an outcome. Since these case numbers are crude, it is very likely that duplicates exist and therefore the actual number of cases may be lower. Selected characteristics are summarized separately for all, serious, and death cases in Table 1. The most frequently reported Preferred Terms listed below reflects labeled events and/or disease-related events.

The sixty-seven death cases were further reviewed; four cases were duplicates. Deaths in 22 cases were related to infection etiology. In the remaining 41 cases, the cause of death appeared to be secondary to the underlying disease, unrelated to the drug, or contained insufficient information.

Table 1. Selected characteristics of all, serious, and death cases

Characteristics	All cases (n=1121)	Serious cases (n=305)	Death cases (n=67)
Age:			
1-<1 mon	1	1	0
1 mon - 5 yrs	0	0	0
6 yrs - 11 yrs	2	0	0
12 yrs - 16 yrs	5	1	0
17 yrs - 20 yrs	4	1	0
21 yrs - 30 yrs	23	6	0
31 yrs - 40 yrs	82	20	1
41 yrs - 50 yrs	170	38	6
51 yrs - 60 yrs	296	67	14
61 yrs - 70 yrs	212	80	21
71 yrs - 80 yrs	113	48	14
81 yrs - 90 yrs	30	19	6
91+	0	0	0
Unknown	183	24	5
Gender:			
Females	881	209	41
Males	197	88	26
Unknown	43	8	

Characteristics	All cases (n=1121)	Serious cases (n=305)	Death cases (n=67)
Report source:			
US	966	182	39
Foreign	154	122	28
Unknown	1	1	
Cases by year and quarter:			
2003 1st quarter	14	8	2
2003 2nd quarter	39	28	6
2003 3rd quarter	480	66	10
2003 4th quarter	488	120	24
2004 1st quarter	100	83	25
Serious outcomes reported*:			
Death	67	67	n/a
Hospitalization	257	257	
Life-threatening	22	22	
Disabled	13	13	
Congenital Anomaly	1	1	
Required intervention	136	136	
Most frequently reported event Preferred Terms (PT) *:	Injection site burning (194) Injection site erythema (91) Injection site pain (67) Headache (64) Rash (59) Nausea (58) Drug ineffective (55) Injection site pruritus (52) Condition aggravated (45) Pyrexia (40) Pruritus (39) Arthralgia (37) Injection site swelling (37) Dizziness (36) Dyspnea (36) Diarrhea (33) Fatigues (33) Peripheral edema (33) Asthenia (31) Injection site rash (31)	Pyrexia (30) Dyspnea (21) Fall (21) Nausea (21) Pneumonia (21) Asthenia (16) Drug ineffective (15) Headache (15) Vomiting (15) Diarrhea (14) Sepsis (14) Cerebrovascular accident (12) Condition aggravated (11) Dizziness (11) Fatigue (11) Abdominal pain (10) Myocardial infarction (10) Peripheral edema (10) Urinary tract infection (10)	Pneumonia (9) Fall (9) Sepsis (8) Dyspnea (7) General physical health deterioration (7) Pyrexia (7) Cardiac arrest (5) Pleural effusion (5) Respiratory failure (5) Staphylococcal infection (5) ARDS (4) Cardiac failure congestive (4) Cerebrovascular accident (4) Coma (4) Death (4) Nausea (4) Peripheral edema (4) Renal insufficiency (4) Vomiting (4)

* More than one possible preferred term per report

5. SUMMARY OF SPECIFIC EVENTS OF INTEREST

PULMONARY EVENTS (N=5)

On June 15, 2004, we conducted a separate search of the AERS database to capture all serious ARDS and ILD cases using the following terms: Lower respiratory tract inflammatory and immunologic conditions (HLT), Parenchymal lung disorders NEC (HLT), Respiratory failures (excl neonatal) (HLT), Respiratory disorders NEC (HLT), and Pulmonary edemas (HLT). The search resulted in 58 cases. We excluded 53 cases for the following reasons: pulmonary event due to other etiology (infection, cancer, post-surgical complication, lupus syndrome, vasculitis, underlying cardiac disease, underlying pulmonary disorder, etc), previous history of pulmonary fibrosis, insufficient information, no temporal relationship, duplicates, and no pulmonary event.

The five cases of notable pulmonary events are summarized in Table 2 of the Appendix: ARDS (1), lymphocytic alveolitis (1), interstitial pneumonitis (1), unspecified inflammatory process of lung (1), and a death due to an unspecified respiratory problem. Three were foreign reports. The time to onset of pulmonary event ranged from two months to a year.

Many confounders exist for many of these cases. An important confounder in all cases is concomitant therapy with MTX, which has been associated with lung injury. The interstitial pneumonitis case with aspergillus on pulmonary biopsy was included in this summary since the reporter considered 'interstitial pneumonitis' to be the serious event and aspergillus as a non-serious event of a nosocomial infection due to the patient's immunosuppressive state. Methotrexate was initiated at the same time as adalimumab in this patient, and despite the reporter's comment, it is possible that aspergillus caused the reported pulmonary event. In the ARDS case, knee surgery was performed about two weeks before the ARDS event, and according to the reporter, the surgery had gone well without major post-operative complications, suggesting that the ARDS event was not a post-surgical complication. The lymphocytic alveolitis case reported a past history of smoking.

Only the interstitial pneumonitis case reported resolution with therapy. Two deaths were reported; ARDS and one death due to an unspecified respiratory problem. The lymphocytic alveolitis event did not resolve at the last follow-up and the outcome of the unspecified inflammatory process of lung was unknown.

HEPATIC/HEPATOBILIARY EVENTS (N=5)

On June 15, 2004, we conducted a separate search of the AERS database for serious hepatic/hepatobiliary events using the reaction group term 'ODS Liver All', which contains all the hepatic and hepatobiliary disorder terms. The search resulted in 36 cases. We excluded 31 cases from final review for the following reasons: elevation of liver function enzymes related to sepsis/infection, unspecified abnormal liver function tests (LFTs)/hepatitis, and no hepatic event.

The five cases of notable hepatic/hepatobiliary events are summarized in Table 3 of the Appendix: four cases of increased liver function enzymes such as AST, ALT and/or alkaline phosphatase (one reported development of autoimmune hepatitis with cirrhosis) and one case of primary biliary cirrhosis (PBC). Three were foreign cases. The time to onset ranged from 2.5 months to 16 months. One patient with unspecified increased AST reported a social history of heavy alcohol drinking.

The PBC case improved with ursodiol therapy, and one case of increased liver function enzymes reported recovery. One death was reported in a patient with ALT elevation; the cause of death was unknown and appeared unrelated to the hepatic event. The outcome was unknown in the other two cases.

RENAL EVENTS (N=2)

On June 15, 2004, we conducted a separate search of the AERS database for potential renal failure cases by using the reaction group term 'ODS Renal Failure', which contains all the renal

insufficiency and renal failure terms. The search resulted in 17 cases, of which 15 cases were excluded for the following reasons: renal failure due to other etiology (sepsis, cardiogenic shock, post-surgical complication, renal cancer), past history of chronic renal failure, and no renal event.

Two cases of renal failures are summarized in Table 4 of Appendix. In one patient, he was concomitantly receiving simvastatin therapy and experienced concurrent rhabdomyolysis, which could have potentially contributed to the renal failure; the renal failure resolved after hemodialysis. The second patient had a history of hypertension and the renal failure had not resolved at the last follow-up.

6. DISCUSSION

As of March 5, 2004, 1121 adverse event reports linked to adalimumab were in the AERS database. The three most commonly reported adverse event terms were injection site (b) (4) injection site erythema, and injection site pain, which are already well known, labeled events. Of 1121 reports, 305 (27%) reports were serious and 67 cases reported death as an outcome. The sixty-seven death cases were further reviewed; four cases were duplicates. Deaths in 22 cases were related to an infectious etiology. In the remaining 41 cases, the cause of death appeared to be secondary to the underlying disease, unrelated to the drug, or contained insufficient information.

The reported adverse event terms from these 1121 cases were reviewed by the DTBIM medical officer.[2] He has requested a more in-depth review of adult respiratory distress syndrome (ARDS) and interstitial lung disease (ILD) cases to determine whether these were disease-related or drug-related. One of each of the following pulmonary events unrelated to other etiology were identified; 1) ARDS, 2) interstitial pneumonitis, 3) lymphocytic alveolitis, 4) unspecified inflammatory process of lungs, and 5) unspecified respiratory problem resulting in death. All patients were concomitantly receiving methotrexate (MTX), an agent that has been well associated with lung injury. In the interstitial pneumonitis case, MTX was initiated at the same time as adalimumab. Only the interstitial pneumonitis case reported resolution with therapy. Two deaths were reported; ARDS and one death due to unspecified respiratory problem. The lymphocytic alveolitis event did not resolve at the last follow-up and the outcome of the unspecified inflammatory process of lung was unknown.

Literature reports[3] have recently raised concerns about possible hepatic injury with similar anti-rheumatic products. Thus, hepatic/hepatobiliary events were also reviewed. Five cases of notable hepatic/hepatobiliary events were found: four cases of increased liver enzymes such as AST, ALT and/or alkaline phosphatase (1 reported development of autoimmune hepatitis with cirrhosis) and one case of primary biliary cirrhosis (PBC). One death was reported in a patient with ALT elevation; the cause of death was unknown and appeared unrelated to the hepatic event. The PBC case improved with ursodiol therapy and the outcome was unknown in the other two cases.

Lastly, renal events were reviewed prompted by one literature case report of nephrotic syndrome associated with the use of adalimumab.[4] However, only two cases of renal failure were

identified and both had risk factors/confounders. The renal failure event abated after drug discontinuation in one patient whereas it had not yet resolved in the other patient.

7. RECOMMENDATION

Our review did not find any serious, unlabeled adverse events and the current label seems to appropriately reflect the postmarketing events to date. We will continue to closely monitor incoming adverse event reports.

8. REFERENCES

1) BLA 125057/16, submission date 10/02/2003.
2) Cases by Primary SOC and PT, standard report from AERS, dated 4/6/2004.
3) Suissa S, Ernst P, Bitton A, and Hidson M. Presentation: The use of leflunomide and other DMARDs in rheumatoid arthritis and the risk of hepatic events. Orlando, FL: American College of Rheumatology: 2003 meeting; October 23-28, 2003: Abstract 781.
4) Broeder AAD, Assmann KJM, van Riel PLCM, Wetzels JFM. Nephrotic syndrome as a complication of anti-TNF alpha in a patient with rheumatoid arthritis. The Netherlands Journal of Medicine 2003; 61: 137-141.
5) Humira (Adalimumab) package insert. Abbott Laboratories, Jan 2003.

Hyon J. Kwon, Pharm.D., M.P.H.

Concur:

Marilyn R. Pitts, Pharm.D., Acting Team Leader

cc:
BLA NO. STN 125057/16
HFM 576 Conner/Liang/Siegel/Walton
HFD-430 Avigan/Pitts/Kang/Division File

Appendix

Table 2. Summary of serious ARDS and ILD cases (N=5)

Event	Age/ Gender (source)	Duration of therapy	Concomitant immuno-suppressants/ Relevant medications	Signs & Symptoms (S/Sx); Diagnostic information	Outcome	Other relevant information
Lymphocytic alveolitis	75 F (Foreign)	9.5 months	MTX (8 yrs), leflunomide (2 yrs), prednisone (yrs)	S/Sx - hypoxia; Bronchoalveolar lavage - lymphocytic alveolitis	Not resolved at last follow-up (few days after the event); on steroid therapy	Past history of cigarette smoking
Interstitial pneumonitis	72 F (Foreign)	4 months	MTX (initiated at the same time as adalimumab)	S/Sx – progressive dyspnea, edema, palpitations; CXR - interstitial pattern bilaterally; pulmonary biopsy - pulmonary lesion, chronic & acute inflammation, negative for malignancy, + for Aspergillus	Resolved with therapy	Reporter stated Aspergillus infection was considered to be non-serious, nosocomial infection that seemed not related to the serious event
ARDS	56 M (Foreign)	12 months	MTX	S/Sx - hypoxic, shortness of breath (SOB); Increased blood carbon dioxide levels with negative blood cultures	Death due to ARDS	Knee surgery 2 weeks before ARDS, but went well with no major post-op complications; history of smoker, COPD
Inflammatory process of lungs (unspecified)	64 F (US)	4 months	MTX (yrs), hydroxy-chloroquine (yrs)	S/Sx - cough, SOB, fever; Bronchoscopy - inflammatory process of lungs, pneumonia ruled out	Unknown	Nonsmoker
Respiratory problem (unspecified)	76 F (US)	2 months	MTX, prednisone	Unknown	Death due to unspecified respiratory problem	

Table 3. Summary of serious hepatic/hepatobiliary cases (N=5)

Event	Age/ Gender (source)	Duration of therapy	Concomitant immuno-suppressants/ Relevant medications	Signs & symptoms; Diagnostic information	Outcome	Other relevant information
Increased ALT	48 F (US)	Unknown exact time frame, but within 1 yr	Prednisone	Unknown	Unknown; died in her sleep sometime later (cause of death unknown)	RA since 1958
Increased AST	61 M (US)	1 year		Unspecified increased AST	Unknown	Heavy alcohol drinker
Increased AST, ALT, and alk phos	58 F (Foreign)	Unknown, but received 4 injections before the event	Prednisone	AST 1438, ALT 1018, alk phos 259, normal hepatic ultrasound	Recovered (AST 27, ALT 26)	Previous history of infliximab use for 2 years
Increased LFTs, then autoimmune hepatitis leading to cirrhosis	58 F (Foreign)	16 months (increased LFTs); 4.5 yrs (dx of autoimmune hepatitis)		Most recently, bilirubin 24 (1-22), alk phos 595 (70-330), AST 776 (5-43), total bilirubin 24 (1-22), ANA + (1/400); liver biosy - autoimmune hepatitis and cirrhosis	Unknown	History of celiac disease
Primary biliary cirrhosis	42 F (Foreign)	2.5 months	MTX (5 yrs), unspecified DMARD (2 yrs), prednisolone	S/Sx - colicky pain, nausea, emesis, steatorrhea; Serology - + for antimitochondrial autoantibodies; ultrasound - negative for PBC; serology - negative for hepatitis	Liver functions improved on ursodiol therapy	RA since 1998, h/o cholelithiasis & cholecystectomy (2002), non-drinker

Table 4. Summary of serious renal cases (N=2)

Event	Age/ Gender (source)	Duration of therapy	Concomitant immuno-suppressants/ Relevant medications	Signs & Symptoms (S/Sx); Diagnostic information	Outcome	Other relevant information
Renal failure, undergoing hemodialysis	30 M (US)	7 days (after one injection)	Simvastatin (~5 yrs)	S/Sx – SOB, dizziness, fatigue, malaise; BUN 134, SCr 13.9, CPK 6471, uric acid 19.0; muscle biopsy normal; Kidney ultrasound - increased echogenicity of renal cortices suggestive of medical renal disease	Event abated	Experienced concurrent rhabdomyolysis
Renal failure	38 F (US)	12 days	MTX, prednisone	BUN 83, SCr 4.2	Not resolved	History of hypertension, RA since 1998

4/26/04

CONSULTATIVE REVIEW

APR 2 6 2004

STN 125057/16.3
SUBMISSION DATE: October 2003
RECEIPT DATE: October 2003
DATE OF CONSULT REQUEST: March 2004
DATE PROPOSED FOR COMPLETION: April 2004

REQUESTOR:	**Name: Li-Ching Liang** **Title: Medical Reviewer** **ODEVI/DTBIMP** **301 594-5643**
SUPERVISOR:	**Jeff Siegel**
PRODUCT:	**Adalimumab**
INDICATION:	**Treatment of Rheumatoid Arthritis**
SPONSOR:	**Abbott**
CONSULTANT:	**Lydia O. Martynec** **Imaging Reviewer** **ODEVI/DTOP** **301 594-5686**
TEAM LEADER:	**Genevieve Schechter, M.D.**
DIVISION DIRECTOR:	**Patricia Keegan, M.D.**
REGULATORY PROJECT MANAGER:	**Beverly Conner**

I. REASON(S) FOR CONSULT REQUEST

Humira was licensed by Abbott on December 31, 2002 for the treatment of severe to moderate Rheumatoid Arthritis. In the submitted Phase 3 continuation study the sponsor has submitted a Year 2 Report of human anti-TNF monoclonal antibody D2E7 in Rheumatoid Arthritis. The sponsor wishes to expand the indication of the current package insert to include improving physical function in adult patients with moderately to severe active rheumatoid arthritis who have an inadequate response to DMARDS and maintain inhibition of structural damage, as measured by the TSS.

This was a multi-center, open label study involving subjects with RA receiving MTX who were previously enrolled in Study DE019, the double blind placebo controlled lead in study. Subjects were eligible to enter Study DE019 OLE if they had completed 52 weeks of therapy on adalimumab or placebo in Study DE019. Subjects who participated in Study DE019 OLE received open label injections of 40 mg adalimumab every other week. The study treatment was continued for up to 104 weeks, as was concomitant MTX treatment.

The analyses of Total Sharp Scores (TSS), Erosion Scores, and Joint Space Narrowing (JSN) scores are presented to evaluate radiographic disease 2 year Follow-up of patients enrolled into the Study DE019 OLE. The sponsor has also submitted the radiographic database as part of the sBLA which is the scope of this review.

The protocol specified that each patient was to have X-rays taken at baseline, Week 24 and Week 52. Subsequently, the Week 24 imaging time point was dropped in a protocol amendment. The X-rays used in the analysis performed by the independent readers were the baseline, Week 52 and Week 104 X-rays for each patient continuing into the study.

The X-rays were scored by 2 readers, blinded to the time sequence of X-rays and to the patient's original treatment in Study DE019 OLE. Readers were presented each patient's case using a computer assisted masked reading method (CAMR) consisting of 2 high resolution monitors and a computerized score sheet incorporating the modified Sharp Scoring Method.

An image set was all the time points for a single image (right-hand-wrist, left hand wrist, right forefoot, left forefoot) for a patient. The CAMR presented to each reader the image sets for each patient in the following order: right hand-wrist, left hand-wrist, right forefoot, and left forefoot. There were two to four time points for each image set. The readers viewed the first image set (i.e., right hand-wrist at each time point) on one monitor to get an overview of the extent of joint damage. The reader was then presented with a strip of joints from each 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 CAMR 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. The scores were entered directly onto the electronic score sheet. Readers were instructed to complete each patient case before going on to the next case. The data from the electronic score sheet was sent to the independent contractor (b) (4), where it was transformed into a SAS data set and sent to the sponsor for correlation with the clinical database.

The primary radiologic endpoint was the sustained inhibition of structural damage for subjects originally receiving Adalimumab in Study DE019. The sustained inhibition of structural damage (radiographic progression) was defined as the change in TSS during the second year of treatment compared to Week 52. The Erosion Score and Joint Space Narrowing Scores for each reader was calculated and the mean score derived. The final Total Sharp Score was defined as the sum of the Erosion and JSN scores.

The secondary radiologic endpoints were the following:

Total Sharp Score
Total Erosions
No Erosion Score Change Between Week 52 and Week 104
Subgroup Analysis of Subjects with Change of Less than or Equal to Zero in Erosion Score at Week 52 and followed to Week 104
Joint Space Narrowing Score Yearly Progression in Total Sharp Score
Rate of change in joint erosions (Modified Sharp Erosion Score over 12 months)

The joint X-rays were scored according to the Modified Sharp Score Method. The original Sharp method scored 27 joints of each hand-wrist for erosions and joint space narrowing. In 1985, the Sharp Method was revised to score 17 joints of each hand-wrist for erosions and 18 joints for Joint Space Narrowing. In 1989, van der Heijde added the 5 metatarsophalangeal (MTP) joints and the first PIP of the forefoot. This method was modified in the protocol so that 17 joints of each hand-wrist and 6 joints of each forefoot will be scored for erosions and 16 joints of each hand wrist and the 5 MTP joints of each forefoot will be scored for joint space narrowing. The original Sharp score for erosions was a scale from 0 to 5 based on the number of erosions in each joint. The original Sharp score for Joint Space Narrowing was on a scale from 0 to 4. The scale for scoring erosions has not been modified for the study and is still on a scale from 0 to 5. However the use of this scale has been changed in that instead of counting discrete erosions (as in the original Sharp score) the use of the scale has been modified such that a one integer increase or decrease in the score for each joint is allowed if there has been a change in the number of erosions or ≤ 20 % change in the area eroded. The Joint Space Narrowing is scored on a scale from 0 to 4 (as in the original Sharp Method) but the first PIP joint of the foot and the radio-ulnar and lunate-triquetrium of the wrist will not be scored for Joint Space Narrowing.

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 10 patients identified by the clinical reviewer.

II. RESPONSES TO REQUESTOR'S ISSUES / OTHER RECOMMENDATIONS / COMMENTS:

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

III. DESCRIPTION OF THE MATERIAL PROVIDED FOR REVIEW:

The sponsor has submitted the 2 Year Image Database for Study DE019 OLE. The image database contains 10 DVD's that contain digitized X-rays for patients enrolled in Study DEO19 OLE.

457 patients were enrolled into Study DE019. Of the 457 patients enrolled, 434 patients had X-rays available during the 2-year window. The X-rays for all patients on whom the Sharp Score was calculated (n= 323) we all available for review.

The [redacted] (b) (4) (CRO) representative successfully loaded the Imaging Database on November 19, 2003.

IV. CONSULTANT'S REVIEW OF MATERIAL PROVIDED BY REQUESTOR WITH CONSULTANT'S COMMENTS:

The reviewer was able to open the full imaging data set consisting of films from 434 patients. The X-rays were viewed with Dr. Liang, the clinical reviewer and [redacted] (b) (4) who was the prior imaging reviewer for Humira at time of licensure and up to and including the 2-year radiographic datasets.

The reviewer was asked by Dr. Liang to review the X-ray films for the following 12 patients: Pt. # 001-01, Pt. # 002-01, Pt. # 004-02, Pt. # 007-06, Pt. # 007-08, Pt.# 009-02, Pt. # 0011-07, Pt. # 0016-003, Pt.# 0018-051904, Pt.# 0011-07, Pt # 0016-03, Pt.# 0018-05.

In addition the reviewer reviewed the X-rays for an additional 24 patients (Pt. # 001-02, P # 002-005, Pt # 002-02, Pt # 039-05, Pt # 039-10, Pt # 039-08, Pt # 012-02, Pt # 005-02, Pt # 004-02, Pt # 020-01, Pt # 030-01, Pt # 051-02, Pt # 073-03, Pt # 073-03, Pt # 080-03, Pt # 86-07, Pt # 089-10, Pt # 091-03, Pt # 092-01, Pt. # 92-07, Pt # 097-15, Pt # 99-01, Pt # 07-03, Pt # 07-11.

The dataset for each patient from year 1 through 2 was complete for all 36 patients reviewed. Images were masked and all time points were identified. The readers were able to validate the reading score of the independent reading score for all of the patients queried.

Several of the patients were noted to have scores with the letters " C", "D", "E" or "F" for the MTP or JSN scores. Review of the protocol regarding the meaning of the above letter scores was not found. The sponsor was called and provided a follow-up amendment with the meaning of these letter code scores. Codes were assigned to joints that could not be evaluated radiographically. The sponsor stated that regardless of the letter code used, if a joint could not be evaluated, then it was set to missing and did not contribute to the Total Sharp Score.

2 patients were found to have minor deficiencies: Pt # 051-02 was found to have a missing baseline image of the right hand (but scoring was recorded) and Pt # 92-07 had a reading performed by Reader 1 only.

In conclusion, in the performance of the quality check on 12 patients identified by the clinical reviewer and an additional 24 patients, the imaging consultant found the data sets to be complete with no major deficiencies identified.

Lydia O. Martin 4/21/04
(Date)
Consultant
Title

Geneen A. Schweitzer MD 4/24/04
(date)
Team Leader

Patricia Keegan (date) 4/26/04
Division Director (DTBOP)

MEMORANDUM

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

DATE: March 24, 2004

TO: Marc Walton, M.D., Ph.D., Director
Division of Therapeutic Biological Internal Medicine Products
HFM-570

VIA: Beverly Conner, Pharm.D., Consumer Safety Officer
Division of Review Management Policy
HFM-588

FROM: Jeanine Best, M.S.N., R.N., P.N.P. 3/24/04
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director JHDepp for G. Dalpan
Division of Surveillance, Research, and Communication Support
HFD-410 3/25/04

SUBJECT: ODS/DSRCS Review of Patient Labeling for Humira (adalimumab) STN 125057/16

Background and Summary

The sponsor submitted an efficacy supplement on September 30, 2003 to expand the product indication to include physical function and quality of life information. Humira has an approved patient package insert (PPI) and the PPI was revised as follows to reflect the expanded indication:

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 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 improve your ability to perform daily activities (b) (4), and may help prevent

further damage to your bones and joints.

Comments and Recommendations:

1. We find the additional language added to the PPI acceptable and patient friendly.

2. Avoid the use of all upper case letters for words and/or statements written in the PI and the PPI (the tradename is an exception). All upper case letters are difficult to read. Bold or increase the font size to emphasize words or statement., e.g.:

Revise
"FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS."
to
"For your protection, it is important that you follow these instructions."
or
"For your protection, it is important that you follow these instructions."

Please call us if you have any questions.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/16

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF NEW DRUGS

OFFICE OF DRUG EVALUATION VI

DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex II, 6th Floor
1451 Rockville Pike
Rockville, Maryland 20852-1448
FAX #: 301-827-5397

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 25 **(Including Cover Page)**

FAX TO: Jim Steck

Facsimile Telephone No. 847 937 8002 **Voice Telephone No.** 847 937 0335

FROM: Beverly Conner

Facsimile Telephone No. 301 827 5397 **Voice Telephone No.** 301 827 4358

DATE: 7/30/04 **TIME:** 12:30 pm

MESSAGE: FDA revised labeling

Forward to: DCC - HFM-99, Woodmont I - 200N

CBER DOCUMENT CONTROL CENTER
FILING INSTRUCTIONS

REGULATORY MATERIALS - BLA RELATED

Instructions:

Fill out this form completely. Firmly attach this form to any documents to be submitted to the DCC for filing.
Send this form with attached documents to the Document Control Center, HFM-99.
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Questions? Call us at the DCC. Phone 827-5940.

Document Type/Description

■ Biologic License Material	☐ Unlicensed Establishment Correspondence
☐ Adverse Event Report	
☐ Product Promotional Material	
☐ Establishment Inspection Report	

Date

7-30-04

Enter as appropriate: Approval date of application or supplement submission
Month/year for Adverse Event, Product Promotional material
Date of Inspection

File Attributes - (List Multiple Application Numbers on attached sheet)

STN - Complete both Levels		Status of Application (Check Appropriate Box)	
First Level	Second Level		
125057	16	■ Approved	☐ Withdrawn
		☐ Revoked	☐ Denied
		☐ Completed	☐ Refusal to File
License Number 0043	☐ Multiple STN Submission (Include list of all STN on separate sheet)		
Description: Supplement: expand the indication to include improving physical function in adult patients with moderate severely active rhematoid arthritis who have had an inadequate response to one or more DMARDS			

Submitted By:

Name	Date Submitted to DCC
Beverly Conner	
Division Mail Code	Telephone Number
HFM-585	7-4358

For DCC Use Only:
Verified By: Filed By:

DCC-121 – 06/02

LICENSING ACTION RECOMMENDATION

Applicant: Abbott Laboratories **STN:** 125057/16

Product:

Adalimumab, Humira

Indication / manufacturer's change :

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

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ☐ Categorical Exclusion

☐ Review of labeling Date completed _____ ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

☐ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____ Date: 7/30/04

Product Office's Responsible Division Director(s)*: _____ Date: 7/30/04

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

☐ Compliance status checked ☐ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) Beverly Conner Date: 7/30/04

Responsible Division Director (where product is submitted, e.g., application division or DMPQ) Jack Dye Date: 7/30/04

Form DCC-201 (05/2003)

FOOD AND DRUG ADMINISTRATION

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Rockville, Maryland 20852-1448
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TOTAL NUMBER OF PAGES: 26 **(Including Cover Page)**

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Facsimile Telephone No. 847 937 8002 **Voice Telephone No.** 847 937 0335

FROM: Beverly Conner

Facsimile Telephone No. 301 827 5397 **Voice Telephone No.** 301 827 4358

DATE: 7/28/04 **TIME:** 3:12 PM

MESSAGE: labeling for STN 125057/16

4:00 Confirmed Jim Steck Received fax. BConner

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0305
RECIPIENT ADDRESS	918479378002
DESTINATION ID	
ST. TIME	07/28 15:11
TIME USE	04'17
PAGES SENT	25
RESULT	OK

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Facsimile Telephone No. 301 827 5397 **Voice Telephone No.** 301 827 4358

DATE: 7/28/04 **TIME:** 3:12 PM

MESSAGE: labeling for STN 125057/16

BLA/NDA/PMA
Review Committee Assignment Memorandum

☐ Initial Assignment
☒ Change

STN: 125057/16

Applicant: Abbott Labs

Product: Adalimumab, Humira

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
	Reviewer	Product*		
	Reviewer	Product*		
	Reviewer	Product		
	Reviewer	Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
	Reviewer	BiMo		
Hyon Kwon	Reviewer	Safety Evaluator	Claudia Korwoski	11/25/03
	Reviewer	CMC, Facility*		
Jeanine Best	Reviewer DSRCS	Labeling	Leslie Stephens	11/25/03
Eva Barrion	DDMAC Rev	[redacted] labeling	Marci Kiester	11/3/03
Catherine Miller	DDMAC Reviewer	labeling	Marci Kiester	7/7/04
Kathleen Uhl	Consult Reviewer	Preg. Labeling	Dianne Kennedy	7/8/04

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
Eva Barrion	DDMAC Reviewer	Labeling	Catherine Miller	7/7/04

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Beverly Conner — Name Printed
Beverly Conner — Signature
7/26/04 — Date

Memo entered in RMS by: _____ Date: _____ QC by: LB Date: 7-29-04

TELECON MEMO

Time/date: 2:300pm-3:00pm, 3/11/04

Attendees
Abbott: Bagyashree Sundaram and Rich Manski.

FDA: Bo Zhen

Subject: Discrepancy between my analysis and the sponsor's in Table 7 sBLA:125057/16, Abbott, Adalimumab

Background before the telecon
The sponsor provided a SAS program by FAX at 5:04pm, 3/8/04 and claimed that this program could allow me to duplicate 87 responders under 20 mg group (LOCF) using the data set they submitted to the Agency.

I found that I was able to duplicate 87, but that some of the other numbers were changed correspondingly and became inconsistent with what are presented in Table 7 using the same variables and observations the program indicates. I was also unable to duplicate the results based on what they suggested in the second meeting. So I called Ms. Sundaram and requested a program that can generate all numbers that are matched with those in Table 7.

The sponsor FAXed me another program on 3/9/04. I also FAXed the sponsor my program and the discrepancies I found. Then we had this telecon for clarification.

Telecon
Dr. Manski said he had looked at my program and commented that I should use a value "ET" under a variable called "visitid" to identify additional HAQ values in the second year study and should use "L_HAQ" instead of "HAQ" since "L_HAQ" represents "LOCF for HAQ"

I said that "ET" was not clearly defined in the database and was never mentioned in the previous two programs and telecons. I also said that I was told not to use "L_HAQ", but "HAQ" in the first telecon.

Dr. Manski explained that the work was transferred to a different statistical group for preparing the submissions. The statisticians who attended the first meeting might not fully understand the structure of the data set submitted to the Agency and might give me inadequate information regarding how to use the variables since they are not familiar with the database submitted to the Agency.

Dr. Manski further explained to me that there were some errors in the second program the sponsor gave me on 3/8/04 because they were in a rush to write the program and send it out. The first program that uses "HAQ" was not useful for me because it was written based on different structures of the database. This was why I was confused. He did not know what was

the rationale they did not include a SAS program that works for the data set submitted to the Agency.

I asked them to hold and let me spend some time in my computer to check "ET" and re-write my program according to the new information they provided. After checking the data set and modify my program according to what he suggested, I finally obtained results that are matched with those in Table 7. I also checked that the results are consistent with different programming approaches by applying "ET" to identify additional HAQ values.

I told them that the issue of discrepancy was resolved.

BS

Telecon Memo

Time/date: 10:00am -10:30am, 3/8/04

Attendees
Abbott: [redacted] (b) (4), [redacted] (b) (4), Shamsul Alam, Jim Steck, Bagyashree Sundaram, George Spencer-Green, and Rich Manski.

FDA: Bo Zhen

Subject: Discrepancy between my analysis and the sponsor's in Table 7 sBLA:125057/16, Abbott, Adalimumab

I pointed out that I have checked the SAS program the sponsor FAXed last week, but was unable to verify the program and the analysis. The program used the key variables that could not be found in the data set submitted. The sponsor explained that the data set they submitted had been simplified for the purpose of easy use for the Agency. They used different data set for generating numbers in Table 7, but claimed that these two data sets should be consistent.

I expressed my concern that there may be some errors when they simplify the data set. The sponsor responded that they have verified the process of simplifying the data set.

I stated that I could not obtain the right results based on what the sponsor suggested in the previous meeting. The sponsor said that the reason I got different number might be due to using the data at week 54. They provided ID numbers (7008, 709, 7701) for the three patients whose last visits were at week 54 and said that we should not carry their values forward since values at week 54 were considered as baseline for the extension study.

I agreed to re-analyze the data based on their new suggestion and said I would contact them with any questions.

BB

Telecon Memo

Time/date: 3:00pm – 3:30pm, 3/4/04

Attendees

Abbott: [redacted] (b) (4), [redacted] (b) (4), Shamsul Alam, Jim Steck, and Bagyashree Sundaram

FDA: Bo Zhen

Subject: Discrepancy between my analysis and the sponsor's in Table 7 sBLA:125057/16, Abbott, Adalimumab

I stated that I was unable to fully duplicate the results presented in Table 7 (results from the primary analysis). The number of 0.5 responder at week 104 (LOCF) under 20 mg group I got using the data set (ACR.xpt) was 90 instead of 87 in Table 7. Although the sponsor included many SAS programs in the sBLA submission, but the one for Table 7 was not submitted. It is difficult for me to verify the discrepancy.

The sponsor asked if I have checked any errors and/or duplicate numbers in my SAS program. I said 'yes'. Later on, we found that the sponsor and I used different programming approaches to analyze the data. I used the variable "L_HAQ" while the sponsor said they used "HAQ". The sponsor suggested that "HAQ" should not be used since it may confuse me. While I agreed to repeat the analysis using the sponsor's approach, I asked the sponsor to do the same analysis using my approach. The sponsor agreed.

I also asked the sponsor to FAX me the SAS program they used for Table 7. They agreed.

BZ

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125057/16

DEC 15 2003

Abbott Laboratories
Attention: Meg Doherty, MPH
Senior Regulatory Administrator
200 Abbott Park Road
D-491, AP-30-1-NE
Abbott Park, IL 60064-6157

Dear Ms. Doherty:

Please refer to the supplement to your biologics license application (BLA) for Adalimumab submitted under section 351 of the Public Health Service Act, and to our filing letter dated December 1, 2003. While conducting our filing review we identified the following potential review issues:

1. The current submission presents Health Assessment Questionnaire (HAQ) data for study DE019 OLE only for patients enrolling into study DE019 OLE. Analysis of this patient group alone may be biased in that it does not include those subjects who dropped out of study DE019 or those subjects who chose not to enroll in study DE019 OLE. Please submit an intent-to-treat analysis of the DE019 OLE HAQ data for all subjects initially randomized in study DE019.

2. You have submitted data on those patients with no x-ray progression from weeks 0-52 (in study DE019) and weeks 52-104 (in study DE019 OLE). This does not allow assessment of the proportion of patients who had no x-ray progression from weeks 0 to 104. Please submit:

   a. Analyses of those patients with no x-ray progression from weeks 0 to 104.

   b. Analyses of the annualized rate of x-ray progression for weeks 0 to 52; weeks 52-104; and weeks 0 to 104.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on 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.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Beverly Conner, Pharm.D., at (301) 827-4358.

Sincerely,

Beverly Conner Pharm.D.

Beverly Conner, Pharm.D.
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Deficiencies Identified (DI)

SS Data Check:
- **Communication**
- **Milestone: Confirm Deficiencies Identified Entry & Closed Date**

cc: Division BLA Files
B. Conner, HFM-588
L. Liang, HFM-582
L. Martyntec, HFM-573
B. Zhen, HFM-219
L. Johnson, HFM-650
E. Barrion, HFD-42

History: B. Conner:123/12/03: K. Townsend: 12.15.2003

File Name:S:\Conner\BLA\125057_16DI

Division	Name/Signature	Date
DRMP	Beverly Conner	12/15/03
DCMP	Kelly Townsend	12/16/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125057/16

DEC 01 2003

Abbott Laboratories
Attention: Jeanne M. Fox
Senior Director, PPD Regulatory Affairs
D-491, AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Fox:

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 September 30, 2003 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 August 1, 2004. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before December 15, 2003.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Beverly Conner, Pharm.D., at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
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**

cc: Division BLA Files
B. Conner, HFM-588
L. Liang, HFM-582
L. Martyntec, HFM-573
B. Zhen, HFM-219
L. Johnson, HFM-650
E. Barrion, HFD-42

History: B. Conner:11/21/03: K. Townsend: 11.26.2003: 12.1.2003

File Name: S:\Conner\BLA\Letters\125057_16FL

Division	Name/Signature	Date
DRMP	B. Conner	12/1/03
DRMP	Dep	12-1-03
DRMP	K. Townsend	12-2-03

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: 125057/16 Product: Adalimumab Applicant: Abbott

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 11/13/03 Committee Recommendation (circle one): (File) RTF

RPM: Beverly Conner
(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):
  - X 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 Bo Zhen _____ _____ _____
- ☐ Memo of Filing Meeting

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)	N/A
if CMC supplement:		
❑ description and results of studies performed to evaluate the change	Y N	N/A
❑ 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? Yes, PMC # original BLA approval ltr 12/31/02

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: B Cenner Branch Chief concurrence:

STN 125057/16 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)	— cross references required BLA submission
❑ 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)	
Labeling:	(Y) N	
❑ PI –non-annotated	(Y) N	
❑ PI –annotated	(Y) N	
❑ PI (electronic)	(Y)	
❑ Medication Guide —	(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	

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	> NA for stat review
❑ 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	> NA for stat review
❑ 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?	If not, action & status
❑ summary reports reference the location of individual data and records ❑ protocols for clinical trials present ❑ all electronic submission components usable	(Y) N (Y) N (Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements ❑ conducted in compliance with requirements for informed consent	(Y) N (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)	More than one trial has shown improvement in physical function. This single trial will show physical function can improvement can be maitained for more than one year
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)	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

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	NA
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	NA
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 report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
DE019	(Y) N	(Y) N NR	(Y) N	Y N NA 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).

NA

Is clinical site(s) inspection (BiMo) needed?

NA

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

Reviewer: [signature] Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)
11/5/03

Concurrence:

Branch Chief: _____ Division. Director: Haka Chakravarty 11/5/03
(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	> 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	
○ electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	N/A

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?	If not, 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	2.
❑ 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	
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	N/A.
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

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 report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
DE019OLE	(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?

No

Is an Advisory Committee needed?

No

Recommendation (circle one): (File) RTF

Reviewer: [signature] 11/13/2003 Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] Division. Director: [signature] 11/18/03
(signature/ date) (signature/ date)
11/13/03

BLA/NDA/PMA
Review Committee Assignment Memorandum

☒ Initial Assignment
☐ Change

STN: 125057/16

Applicant: Abbott

Product: Adalimumab

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Beverly Conner	Reg. Project Manager	Admin/Regulatory	K Schneider	10/16/03
	Reviewer	Admin/Regulatory		
	Reviewer	Product*		
	Reviewer	Product*		
	Reviewer	Product		
Li Liang	~~Reviewer~~ Chairperson	Clinical	J. Siegel	10/7/03
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
Bo-Guang Zhen	Reviewer	Biostatistics	C. Aneiro	10/9/03
Lloyd Johnson	Reviewer	BiMo	Khin U	10/8/03
	Reviewer	Safety Evaluator		
	Reviewer	CMC, Facility*		
		Labeling		
Lydia Martynec	Reviewer	Other	G. Mills	10/6/03

*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:

Beverly Conner (Name Printed) Beverly Conner (Signature) 10/9/03 (Date)

Memo entered in RMS by: DCS Date: 11/3/03 QC by: LB Date: 11/3/03

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

From: Beverly Conner, Pharm.D.,

Date & Time: October 30, 2003, 2:30 - 3:3 0 PM

Subject: **First Committee Meeting for (STN) 125057/16**

Sponsor: **Abbott Laboratories**

Product: **Adalimumab**

Indication: **Current indication: For reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.**
*Expanded will 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

Attendees: Jeffrey Siegel, Beverly Conner, Bo-Guang Zhen, J. Li Liang, Lydia Marytec

Review Schedule Designation: Standard (10 month)

Review Committee:
Chairman and Clinical Reviewer - Li Liang
Clinical Reviewer - Jeffrey Siegel
Statistical Reviewer - Bo-Guang Zhen
Consult Clinical - Lydia Martynec
BIMO Reviewer- Lloyd Johnson
RPM - Beverly Conner

Agenda Items:

1. The role members of the committee members was briefly discussed.

2. Accessibility to the electronic file: The direct link will be forwarded to all reviewers when the supplement is re-loaded. The road-map was placed in the incorrect folder so it was not usable. The company was contacted and asked to send in corrected files. These

corrected files will also contain the CRFs. The file is still under the DCC log-in number, the linking to the submission did not properly occur. Correction has been requested, Dan Offriga is aware of the problem.

3. Advisory committee will not be needed.

4. Filing meeting should be scheduled.

5. J. Lloyd Johnson and Li Liang should meet in the near future to determine the clinical sites that should be inspected for biomedical monitoring compliance. A DIS consult form will need to be filled out by the RPM once the sites are determined.

6. Committee agrees that a Pharm/tox reviewer is not necessary.

7. DDMAC and ODS consults are being obtained. ODS will be requested to do a review of all postmarketing adverse events.

8. The following milestones for BLA supplement were discussed:

   Milestones for **STN 125057/16**
   Filing Meeting – November 16, 2003
   Filing Action - December 1, 2003 (non-flexible)
   Mid-Cycle – Mid-March 2004
   Deficiencies Identified: December 15, 2003
   Action Due Date – August 1, 2004 (non-flexible)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

OCT 16 2003

Abbott Laboratories
Attention: Jeanne Fox
Senior Director
200 Abbott Park Road
D491, AP30-1E
Abbott Park, IL 60064-6157

Dear Ms. Fox:

SUBMISSION TRACKING NUMBER (STN) BL 125057/16 has been assigned to your recent supplement to your biologics license application for Adalimumab received on October 2, 2003, to 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.

All future correspondence or supportive data relating to this supplemental application should bear the above STN. The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

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, Beverly Conner, at (301) 827-4358.

Sincerely,

Earl S. Dye, Ph.D.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

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