CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 125057/45

Trade Name: Humira®

Generic Name: adalimumab

Sponsor: Abbott Laboratories

Approval Date: 10/03/2005

Indication: Request to supplement biologics license application for adalimumab to expand indication to include psoriatic arthritis was approved.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	**x**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**x**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	**x**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**x**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**x**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/45

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125057/45

OCT 03 2005

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

Dear Mr. Steck:

Your request to supplement your biologics license application for adalimumab to expand the indication to include psoriatic arthritis 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 waiving the pediatric study requirement for this application.

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

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

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

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

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

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

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

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/45

LABELING

(No. 3799)
NEW

HUMIRA®
(adalimumab)

Rx only

Tear at Perforation to Dispense Patient Information

WARNING

RISK OF INFECTIONS

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

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

DESCRIPTION

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

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

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

CLINICAL PHARMACOLOGY

General

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis and psoriatic arthritis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases.

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

Pharmacodynamics

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

Pharmacokinetics

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

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

Adalimumab mean steady-state trough concentrations of approximately 5 μg/mL and 8 to 9 μg/mL, were observed without and with methotrexate (MTX) respectively. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

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

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

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

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

HUMIRA has not been studied in children.

Drug Interactions

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

CLINICAL STUDIES

Rheumatoid Arthritis

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

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

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

Study III evaluated 619 patients who had an inadequate response to MTX. Patients received placebo, 40 mg of HUMIRA every other week with placebo injections on alternate weeks, or 20 mg of HUMIRA weekly for up to 52 weeks. Study III had an additional primary endpoint at 52 weeks of inhibition of disease progression (as detected by X-ray results). Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of HUMIRA was administered every other week for up to 104 weeks.

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

Study V evaluated 799 patients with moderately to severely active rheumatoid arthritis of less than 3 years duration who were ≥18 years old and MTX naïve. Patients were randomized to receive either MTX (optimized to 20 mg/week by week 8), HUMIRA 40

mg every other week or HUMIRA/MTX combination therapy for 104 weeks. Patients were evaluated for signs and symptoms, and for radiographic progression of joint damage. The median disease duration among patients enrolled in the study was 5 months. The median MTX dose achieved was 20 mg.

Clinical Response

The percent of HUMIRA treated patients achieving ACR 20, 50 and 70 responses in Studies II and III are shown in Table 1.

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

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

* $p<0.01$, HUMIRA vs. placebo

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

The results of the components of the ACR response criteria for Studies II and III are shown in Table 2. ACR response rates and improvement in all components of ACR response were maintained to week 104. Over the 2 years in Study III, 20% of HUMIRA patients receiving 40 mg every other week (eow) achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

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

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

[a] 40 mg HUMIRA administered every other week

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

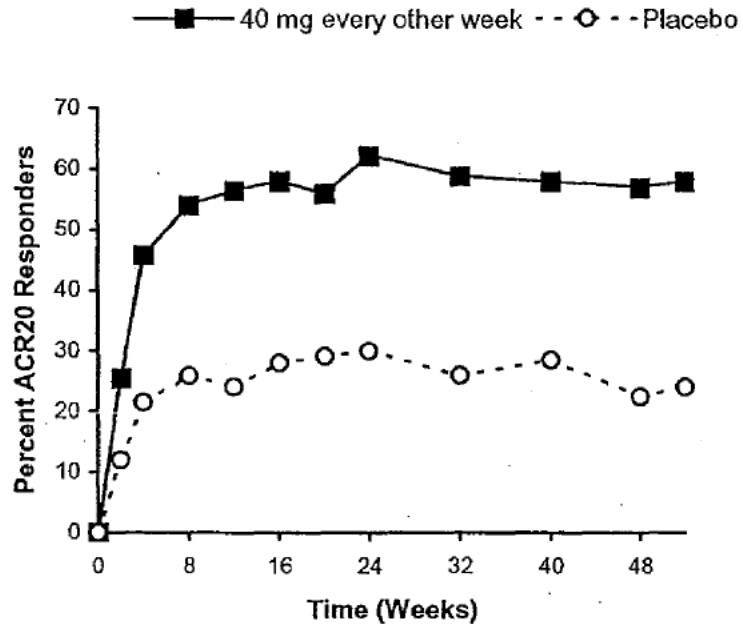
[c] Disability Index of the Health Assessment Questionnaire[2]; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

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

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

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

Figure 1: Study III ACR 20 Responses over 52 Weeks



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

In Study V with MTX naïve patients with recent onset rheumatoid arthritis, the combination treatment with HUMIRA plus MTX led to greater percentages of patients achieving ACR responses than either MTX monotherapy or HUMIRA monotherapy at Week 52 and responses were sustained at Week 104 (see Table 3).

Table 3: ACR Response in Study V (Percent of Patients)

Response	MTX[b] N=257	HUMIRA[c] N=274	HUMIRA/MTX N=268
ACR20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR50			
Week 52	46%	41%	62%

Week 104	43%	37%	59%
ACR70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response [a]	28%	25%	49%

[a] Major clinical response is defined as achieving an ACR70 response for a continuous six month period

[b] $p<0.05$, HUMIRA/MTX *vs.* MTX for ACR 20

[c] $p<0.001$, HUMIRA/MTX *vs.* MTX for ACR 50 and 70, and Major Clinical Response

$p<0.001$, HUMIRA/MTX *vs.* HUMIRA

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

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, at month 12 compared to baseline. At baseline, the median TSS was approximately 55 in the placebo and 40 mg every other week groups. The results are shown in Table 4. HUMIRA/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks.

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

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

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

In the open-label extension of Study III, 77% of the original patients treated with any dose of HUMIRA were evaluated radiographically at 2 years. Patients maintained inhibition of structural damage, as measured by the TSS. Fifty-four percent had no progression of structural damage as defined by a change in the TSS of zero or less.

In Study V, structural joint damage was assessed as in Study III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the HUMIRA/MTX combination group as compared to either the MTX or HUMIRA monotherapy group at Week 52 as well as at Week 104 (see Table 5).

Table 5: Radiographic Mean Change* in Study V

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

* mean (95% confidence interval)

[a] $p<0.001$, HUMIRA/MTX *vs.* MTX at 52 and 104 weeks and for HUMIRA/MTX *vs.* HUMIRA at 104 weeks

[b] $p<0.01$, for HUMIRA/MTX *vs.* HUMIRA at 52 weeks

Physical Function Response

In studies I-IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by The Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

In Study III, the mean (95% CI) improvement in HAQ-DI from baseline at week 52 was 0.60 (0.55, 0.65) for the HUMIRA patients and 0.25 (0.17, 0.33) for placebo/MTX ($p<0.001$) patients. Eighty-two percent of HUMIRA-treated patients who achieved a 0.5 or greater improvement in HAQ-DI at week 52 in the double-blind portion of the study maintained that improvement through week 104 of open-label treatment. Improvement in SF-36 was also maintained through week 104.

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

Psoriatic Arthritis

The safety and efficacy of HUMIRA was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. Study PsA-I enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of ≤30 mg/week for >1 month) could continue MTX at the same dose. Doses of HUMIRA 40 mg or placebo every other week were administered during the 24-week double-blind period of the study.

Compared to placebo, treatment with HUMIRA resulted in improvements in the measures of disease activity (see Tables 6 and 7). Among patients with psoriatic arthritis who received HUMIRA, the clinical responses were apparent in some patients at the time of the first visit (two weeks). Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

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

Table 6: ACR Response in PsA I (Percent of Patients)

Response	Placebo N=162	HUMIRA* N=151
ACR20		
Week 12	14%	58%
Week 24	15%	57%
ACR50		
Week 12	4%	36%
Week 24	6%	39%
ACR70		
Week 12	1%	20%
Week 24	1%	23%

* p<0.001 for all comparisons between HUMIRA and placebo

Table 7: Components of Disease Activity in PsA-I

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

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

[a] Scale 0-78

[b] Scale 0-76

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

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

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

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

INDICATIONS AND USAGE

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with MTX or other DMARDs.

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

CONTRAINDICATIONS

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

WARNINGS

SERIOUS INFECTIONS

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

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

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

Use with Anakinra

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

Neurologic Events

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Malignancies

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

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

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

Hypersensitivity Reactions

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

Hematologic Events

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA (see **ADVERSE REACTIONS, Other Adverse Reactions**). The causal relationship of these reports to HUMIRA remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS

Information to Patients

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

Tuberculosis

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

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

Patients with Heart Failure

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

Immunosuppression

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

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

Immunizations

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

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies**).

Drug Interactions

Methotrexate

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

Anakinra

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

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

ADVERSE REACTIONS

General

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

- Serious Infections
- Neurologic Events
- Malignancies

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

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

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

Infections

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

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

Malignancies

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

Autoantibodies

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

Immunogenicity

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

week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

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

Table 8 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.

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

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

Upper respiratory infection	17	13
Sinusitis	11	9
Flu syndrome	7	6
Gastrointestinal		
Nausea	9	8
Abdominal pain	7	4
Laboratory Tests*		
Laboratory test abnormal	8	7
Hypercholesterolemia	6	4
Hyperlipidemia	7	5
Hematuria	5	4
Alkaline phosphatase increased	5	3
Other		
Injection site pain	12	12
Headache	12	8
Rash	12	6
Accidental injury	10	8
Injection site reaction**	8	1
Back pain	6	4
Urinary tract infection	8	5
Hypertension	5	3

* 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 rheumatoid arthritis 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

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

Adverse Reaction Information from Spontaneous Reports:

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

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

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

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis.

Skin reactions: cutaneous vasculitis.

OVERDOSAGE

The maximum tolerated dose of HUMIRA has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

Storage and Stability

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

HOW SUPPLIED

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

Patient Use Syringe Carton

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

Institutional Use Syringe Carton

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

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

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HUMIRA®
(adalimumab)
Patient Information

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

What is HUMIRA?

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

How does HUMIRA work?

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

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

Who should not take HUMIRA?

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

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

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

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

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

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

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

- If you are scheduled to have major surgery.

- If you are scheduled to be vaccinated for anything.

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

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

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

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

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

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

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

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

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

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

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

What are the other more common side effects with HUMIRA?

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

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

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

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

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

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

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

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

How do I take HUMIRA?

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

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

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

Is one time better than another for taking HUMIRA?

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

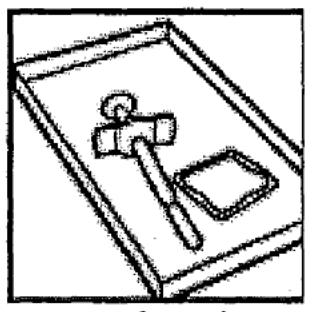
What do I need to do to prepare and give an injection of HUMIRA?

1) Setting up for an injection

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

You will need the following items for each dose:

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



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

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

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

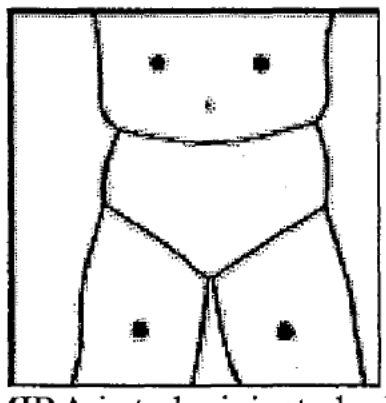
FOR YOUR PROTECTION, IT IS IMPORTANT THAT YOU FOLLOW THESE INSTRUCTIONS.

2) Choosing and preparing an injection site

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

- Choose a different site each time you give yourself an injection. Each new injection should be given at least one inch from a site you used before. Do NOT inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks.

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



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

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

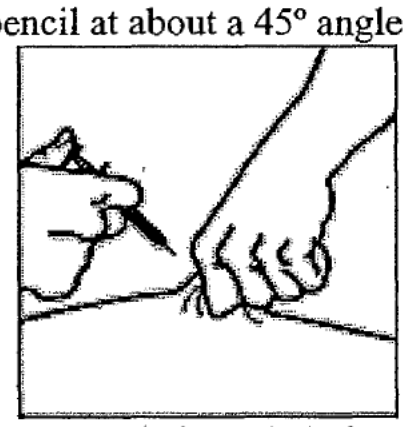
- Hold the syringe upright with the needle facing down. Check to make sure that the amount of liquid in the syringe is the same or close to the 0.8 mL line shown on the pre-filled syringe. The top of the liquid may be curved. If the syringe does

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

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

4) Injecting HUMIRA

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



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

5) Disposing of syringes and needles

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

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

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

HOW DO I STORE HUMIRA?

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

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

Revised: ~~July, 2004~~NEW

ABBOTT
LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/45

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Submission Number	125057/45
Submission Date	December 15, 2004
Receipt Date	December 16, 2004
PDUFA Goal Date	October 16, 2005
Reviewer Name	Rosemarie Neuner, MD, MPH
Review Completion Date	September 27, 2005
Through	Marc Walton, MD, PhD Director DTBIMP and
	Jeffrey Siegel, MD Clinical Team Leader
Established Name	Humira®
(Proposed) Trade Name	Adalimumab
Therapeutic Class	TNF antagonist
Applicant	Abbott Laboratories
Priority Designation	S
Formulation	Injectable
Dosing Regimen	40 mg SC every other week
Indication	Psoriatic Arthritis
Intended Population	Psoriatic Arthritis

Table of Contents

1 Executive Summary

1.1 Recommendation on Regulatory Action

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

1.2 Recommendation on Postmarketing Actions

Based on the review of the efficacy supplement, no post-marketing studies are required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical data submitted in support of a clinical indication for adalimumab as a treatment for psoriatic arthritis were generated from two Phase III trials, Studies M02-518 and 570. These studies were double-blind, multicenter, randomized, placebo-controlled trials in 413 patients with active psoriatic arthritis on a variety of disease modifying agents that evaluated the efficacy and safety of adalimumab 40 mg subcutaneously every other week versus placebo injections over 12 and 24 weeks. The sponsor submitted long-term safety data comprised of up to 72 weeks of continuous treatment with adalimumab generated in the open-label extension trial, Study M02-537, which enrolled 395 patients who completed either Phase III study. All three studies were conducted by the sponsor of this application, Abbott Laboratories.

1.3.2 Efficacy

Studies M02-518 and 570 demonstrated the clinical efficacy of adalimumab as measured by the signs and symptoms endpoint, the ACR 20 response at Week 12 in both studies, and the radiographic co-primary endpoint the modified total Sharp score at Week 24 in Study M02-518. In the pivotal trial, Study M02-518, the ACR 20 response rate was 58% for patients treated with adalimumab versus 14% for the placebo group at Week 12 ($p<0.001$). The ACR 20 response rate in Study M02-570 was 39% for adalimumab treated patients as compared to 16% for the placebo group at Week 12 ($p=0.012$). For the radiographic co-primary endpoint in the pivotal study, the change in modified Sharp score (mTSS) at Week 24 using an intent-to-treat analysis with imputation of missing data was 1.0 for the adalimumab group versus 1.6 for the placebo group ($N=313$; $p<0.001$). The change in mTSS for the subset of subjects who had x-rays at baseline and Week 24 ($N=296$) was -0.2 for the adalimumab group as compared to 1.0 for the placebo group ($p<0.001$).

A variety of prespecified ranked secondary parameters also demonstrated efficacy of adalimumab on various other aspects of psoriatic arthritis during these trials as follows: the

ACR 50 and 70 response rates, the disability index of the HAQ (HAQ-DI), the PASI 50/75, and the physician's global assessment for psoriasis. In Study M02-518 the ACR 50 response rate was 36% and 39% for the adalimumab group as compared to 4% and 6% for the placebo group at Weeks 12 and 24, respectively ($p<0.001$). The Week 12 ACR 50 and 70 response rates in Study M02-570 were 25% and 14% respectively versus 2% and 0% in the placebo group ($p<0.001$). The change in the HAQ-DI in Study M02-518 at Weeks 12 and 24 was 0.5 units for adalimumab treated patients versus 0.0 units for the placebo group ($p<0.001$) while in Study M02-570 the change in score was 0.4 units for the adalimumab group compared to 0.1 units for placebo treated patients ($p=0.008$). Improvement in patients' skin lesions was assessed by the PASI 50 and 75 in Study M02-518 and by the physician's global assessment for psoriasis in both studies. The PASI 50 and 75 responses at Week 12 in Study M02-518 were 72% and 49% respectively for the adalimumab group and 15% and 4% for the placebo group ($p<0.001$). Both of these responses were maintained out to Week 24 ($p<0.001$). In terms of the physician's global assessment for psoriasis (PGA), 62% of the subgroup of adalimumab patients in the pivotal study had clear or almost clear evaluations as compared to 3% of the placebo treated patients at Week 12 ($p<0.001$). At Week 24, this response rate had improved to 71% for the adalimumab group and 12% for the placebo group ($p<0.001$). In Study M02-570, the adalimumab group response rate for PGA assessment for clear or almost clear was 41% versus 7% for the placebo subgroup ($p<0.001$).

The results of other unranked secondary and ancillary parameters that were assessed during these studies such as the individual core components of the ACR20, PsARC, target lesion assessment, the physical component summary of the SF-36, FACIT Fatigue scale, and the Dermatology Life Quality Index also supported the effectiveness of adalimumab as a treatment for psoriatic arthritis in these studies.

1.3.3 Safety

The overall safety profile of the adalimumab psoriatic arthritis database was similar to what has been observed in previous clinical studies with the product in RA patients. No new potential safety signals were identified during the examination of these data. The observed incidence of both serious and severe adverse events was low in both controlled studies and in the combined evaluable patient population exposed to the product. The observed incidence of infectious adverse events was similar to what has been reported in other studies with adalimumab. A total of 4 malignancies (2 cases of lymphoma, 1 case of prostate cancer and 1 case of neuroendocrine carcinoma of the skin) occurred in patients while participating in the open-label extension study. The cases of lymphoma are not unexpected given the product's immunosuppressive properties and an appropriate warning is already listed in the current approved label. Additionally, no TNF-inhibitor class specific adverse events such as tuberculosis/granulomatous infections, demyelinating disorders, drug-induced lupus, or congestive heart failure were observed during the course of these studies. Although more adalimumab treated patients were observed to have elevated liver function tests than in the placebo group, these events were transient in nature and all occurred in patients who were taking concomitant hepatotoxic drugs such as methotrexate, nonsteroidal anti-inflammatory drugs and statins.

2 Introduction and Background

2.1 Product Information

Adalimumab is an anticytokine product that is a member of the tumor necrosis factor (TNF) blocking class of agents. It is a recombinant, human IgG1 monoclonal antibody composed of 1330 amino acids with a molecular weight of approximately 148 kilodaltons. Adalimumab blocks the binding of the proinflammatory cytokine TNF-α to its receptor. A dosage regimen of 40 mg of adalimumab given as a subcutaneous (SC) injection every other week (eow) in patients with PsA was clinically evaluated by the sponsor in this submission. This is the same dose and regimen for which the product is currently approved for the treatment of adult rheumatoid arthritis (RA).

2.2 Currently Available Treatment for Indications

Besides photochemotherapy, there are numerous small molecular entities and a TNF- antagonist that are utilized in the treatment and management of patients with PsA. These products may be given alone or in combination with each other depending on disease severity and include: nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, methotrexate (MTX), leflunomide, sulfasalazine, gold salts, azathioprine, cyclosporine, mycophenolate mofetil, corticosteroids (topical, systemic or as intra-articular injections), systemic retinoids, Vitamin D derivatives, etanercept, and infliximab. Each of these therapies is associated with significant toxicities.

2.3 Availability of Proposed Active Ingredient in the United States

Adalimumab is an approved product that is already available and marketed in the U. S. for patients with rheumatoid arthritis.

2.4 Important Issues With Pharmacologically Related Products

Serious adverse events associated with the use of TNF-antagonist class of biologics include increased susceptibility to opportunistic infections, tuberculosis, demyelinating disorders and malignancies, particularly lymphomas.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

Clinical data reviewed in support of this BLA submission were generated from the following sources:

1) The final study report for Protocol M02-518, a clinical trial conducted in the United States and Europe by the sponsor entitled: A Phase III Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab (D2E7) in Subjects with Moderate to Severely Active Psoriatic Arthritis.
2) The final study report for Protocol M02-570, another international clinical trial conducted by the sponsor entitled: A Phase III Multicenter Study of the Safety and Efficacy of Human Anti-TNF Monoclonal Antibody Adalimumab (D2E7) in Moderate to Severely Active Psoriatic Arthritis Subjects with Inadequate Response to Disease Modifying Anti-Rheumatic Drug Therapy.
3) An interim clinical trial report of the first 24 weeks of the ongoing open-label extension study Protocol M02-537 comprised of patients who had completed either of the 2 preceding studies entitled: A Multi-Center Continuation Trial for Patients Completing Study M02-518 and M02-570 of the Human Anti-TNF Monoclonal Antibody Adalimumab (D2E7) in Patients with Moderate to Severely Active Psoriatic Arthritis.

Although Protocol M02-518 required that patients have bilateral hand and feet x-rays at their baseline and exit study visits, these films were not included in the submission for agency review in support of a structural inhibition claim for adalimumab in PsA. The sponsor intends to submit these data at a later time.

Tables of Clinical Studies

As part of their clinical development program for adalimumab as a therapeutic modality for PsA, the sponsor conducted two double-blind, placebo controlled studies and an open-label continuation study which are summarized in the following Table 1:

Table 1 – Tabular Summary of Clinical Studies Evaluating Adalimumab as a Treatment for PsA

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Inclusion Criteria	Primary Endpoints (EP)	Study Status
Protocol M02-518 **Objectives:** Evaluate the safety and efficacy of adalimumab in patients with active polyarticular PsA on MTX and suboptimal response/ intolerance to NSAID therapy	Multicenter, randomized, double-blind, placebo-controlled, 24-week comparative study. Entry stratified by MTX use and extent of psoriasis (≥ 3 % or < 3% BSA) 50 sites in the United States, Canada, Italy, Germany, France, United Kingdom, Austria, and Belgium	Adalimumab 40 mg via subcutaneous (SC) injection every other week (eow); Placebo SC injection eow **Early escape:** Week 12 – Subjects from either group with ≤ 20% improvement from baseline in both tender and swollen joint counts permitted to take corticosteroids or DMARDs while continuing blinded study medications for the remainder of the trial	N =313 **Adalimumab Group:** 151 enrolled; 140 completed **Placebo Group:** 162 enrolled; 149 completed	Moderate to severe PsA with ≥ 3 tender joints and ≥ 3 swollen joints despite a minimum of 3 months of therapy with doses ≤ 30 mg/week of MTX stable for 4 weeks prior to baseline visit with failure to respond or intolerance to NSAIDs. Stable concomitant doses of ≤ 10 mg/day of prednisone or equivalent permitted	**Co-primary EP:** 1. Proportion of subjects achieving an ACR20 response at Week 12. 2. Mean change over baseline score in the modified total Sharp scores (sum of erosions and joint-space narrowing) of the hands and feet at Week 24	Completed. Final study report included for review.
Protocol M02-570 **Objectives:** Evaluate the safety and efficacy of adalimumab in patients with active polyarticular PsA with inadequate response to DMARD therapy	Multicenter, randomized, double-blind, placebo-controlled, 12-week comparative study. Entry stratified by DMARD use (yes, no) 16 sites in the United States and Canada	Adalimumab 40 mg via SC injection eow; Placebo SC injection eow	N =100 **Adalimumab Group:** 51 enrolled; 50 completed **Placebo Group:** 49 enrolled; 46 completed	Moderate to severe PsA with ≥ 3 tender joints and ≥ 3 swollen joints despite a minimum of 3 months of DMARD therapy stable for 4 weeks prior to baseline visit. Stable concomitant doses of ≤ 10 mg/day of prednisone or equivalent permitted	Proportion of subjects achieving an ACR20 response at Week 12	Completed. Final study report included for review.
Protocol M02-537 **Objectives:** Evaluate the long-term safety and efficacy of adalimumab	Multicenter, uncontrolled, open-label continuation study in subjects who completed Protocol M02-518 or M02-570	Adalimumab 40 mg SC eow Dose escalation to 40 mg sc weekly was permitted in subjects with ≤ 20% improvement from baseline in both TJC and SJC at Week 12 visit	N= 395	Subjects with PsA who completed Protocols M02-518 or M02-570	N/A	Ongoing. Data from patients who had completed Week 24 visit as of 5/17/04 cut-off date

4.3 Review Strategy

This medical officer reviewed Studies M02-518 and M02-570 for efficacy and safety. Additionally, I reviewed the interim report for the first 24-weeks of ongoing Study M02-537 in support of long term safety following prolonged exposure to the product. The primary efficacy analyses and the major secondary analyses of Studies M02-518 and -570 were confirmed by the statistical reviewer.

4.4 Data Quality and Integrity

Two clinical sites that participated in the clinical studies in this submission were audited by the FDA's Division of Scientific Investigations (DSI). The selection of these sites for bioresearch monitoring inspection (BIMO) was based on the large numbers of patients they had enrolled into the pivotal trial, (Study M02-570) and participation by the latter site in the second clinical study (Study M02-518). One site which entered 16 patients into the pivotal study was found to be in compliance with FDA regulations regarding the conduct of clinical investigations. Although the second site which entered 10 patients into Study M02-570 and 4 patients into Study M02-518, was also found to be in compliance with FDA regulations, some minor items were identified during the inspection and discussed with the investigator as follows: 1. the use of a prohibited concomitant medication and incomplete documentation practice in one subject; 2. two instances of transcription errors between source document and CRFs in at least two subjects. The BIMO investigator concluded that neither of these inspectional items impacted on the validity or reliability of the data generated from this site.

4.5 Compliance with Good Clinical Practices

Both Studies M02-518 and 570 were conducted as per the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. A contract research organization (b) (4) was hired by the sponsor to independently monitor participating study sites during the course of the trial. To ensure that investigators were in compliance with the trials' protocols and regulations, a study monitor assigned to each trial was responsible for conducting site audits of all study related documents (including the informed consents signed by subjects) and medications. As a result of these audits, 19 and 17 major protocol deviations were identified to have occurred during the course of Studies M02-518 and 570, respectively, and are shown in Table 2:

Table 2 – Tabular Summary of Major Protocol Deviations for Studies M02-518 and M02-570

Protocol Deviation	Study M02-518		Study M02-570	
	Placebo (N=162)	Adalimumab (N=151)	Placebo (N=49)	Adalimumab (N=51)
Did not satisfy entry criteria	4 (3%)	8 (5%)	2 (4%)	4* (8%)
Received the wrong treatment or incorrect does	2 (1%)	1 (1%)	1 (2%)	0
Received excluded concomitant medication	3 (2%)	1 (1%)	8 (16%)	4* (8%)

*Subjects may be counted in more than one protocol deviation parameter. Two subjects in the adalimumab treatment group, Subject 401 and Subject 352 did not satisfy entry criteria and received an excluded concomitant medication.

Further examination of the data in this submission revealed a protocol violation of the entry criteria that was not captured in the above table. This involved Subject 2542 who was randomized to the adalimumab treatment group in Study M02-518. This patient was discovered to have a delayed reaction to PPD skin testing after receiving two doses of study drug. The investigator decided to withdraw the patient from the trial rather than initiating treatment with prophylactic therapy for TB.

Other protocol violations that may have affected the results of Study M02-518 that were identified during review of this submission include:

- At Site 40 in Belgium, the integrity of the joint assessor's blind may have been compromised while performing other study evaluations for 5 placebo treated and 8 adalimumab treated patients.
- The administration of study rescue medication to 6 placebo-treated patients and 1 adalimumab-treated patients who failed to meet rescue criteria as per the trial protocol

Sensitivity analyses performed by the sponsor demonstrated that excluding study data associated with the above protocol deviations did not affect the outcomes of the study's major endpoints. This finding was validated by the agency's statistical reviewer.

4.6 Financial Disclosures

Financial disclosure was reviewed and deemed to be complete. Although no clinical investigator had a proprietary interest in this product nor a significant equity in the sponsor as defined in 21CFR 54.2(b), two investigators, [redacted] (b) (6) and [redacted] (b) (6), who participated in Study M02-518 received payments from Abbott Laboratory unrelated to their work on this study. [redacted] (b) (6) received payments totaling approximately $30,000 for consulting, honoraria for lectures, and payments for clinical trials other than Study M02-518. [redacted] (b) (6) received payments totaling approximately $40,000 as part of a grant to [redacted] (b) (6) University to help fund an interdisciplinary education program in immune-related diseases. To minimize the potential introduction of bias, the design of Protocol M02-518 utilized an independent assessor to perform joint exams that were integral to the evaluation of the key efficacy variables as well as a central laboratory to conduct lab tests essential to the study. Additionally, the sponsor conducted a subgroup analysis of the study's primary efficacy endpoint that excluded subjects from the 2

study sites identified above where the investigators received additional payments from Abbott Laboratory. The results from this subgroup analysis were similar to those obtained from the analysis of the full study population. This latter analysis was verified as accurate by the agency's statistician.

6 Integrated Review of Efficacy

6.1 Indication:

Psoriatic Arthritis (PsA)

6.1.1 Methods

Efficacy data contained in the submission generated from Studies M02-518 and 570 were reviewed to assess the sponsor's licensing application. Analyses of the individual components of the composite efficacy endpoints and pertinent subgroup analyses were also conducted for both studies. All primary and major secondary analyses were confirmed by the FDA's statistical reviewer.

6.1.2 General Discussion of Endpoints

Presently no FDA guidance document exists for sponsors to use as a reference tool during the development of products for the treatment of PsA. Besides affecting the skin, this disease affects the joints in a manner similar to that seen in RA. Thus, many of the validated assessments employed in psoriasis and RA trials have been previously accepted by the agency for the evaluation of outcomes in PsA studies. At the May 2004 OMERACT 7 Meeting, discussions were held regarding the development of a core set of measures to be used in clinical trials in PsA. The following is a partial listing of domains identified by the panel of rheumatologists and clinical investigators for evaluation in PsA studies: joint activity, patient global, pain assessment, physical assessment, skin disease, quality of life, structural damage, acute phase reactant, enthesitis, dactylitis, and physician global. The American College of Rheumatology (ACR) 20, 50 and 70 response criteria, the Psoriatic Arthritis Response Criteria (PsARC) and the disease activity score (DAS) are composite indexes that were also recommended at this meeting for use as efficacy assessments in studies of this disease. Studies M02-518 and 570 assessed ACR 20, 50 and 70 responses as well as PSARC to evaluate the effect of adalimumab on joint signs and symptoms. Thus the endpoints evaluated in these studies are well acceptable endpoints that are adequate to assess signs and symptoms of PsA.

Both studies evaluated the Psoriasis Area Scoring Index (PASI), a validated composite index used in assessing skin manifestations of psoriasis. It is a based on a weighted average score generated from the percentage of body surface area from plaque involvement of four anatomical sites (head, upper extremities, trunk, and lower extremities).

The modified Total Sharp Score (TSS) is a validated x-ray scoring system generated from blinded evaluation of bilateral radiographic images of the hands and feet involving 21 bilateral hand/wrist joints and 6 bilateral foot joints. The agency has previously accepted results of TSS in the assessment of progression of joint damage in psoriatic arthritis. Given the chronic nature of the disease and the slow rate of progression of structural damage, the agency has generally based a radiographic claim in PsA on 1-year data.

6.1.3 Study Design

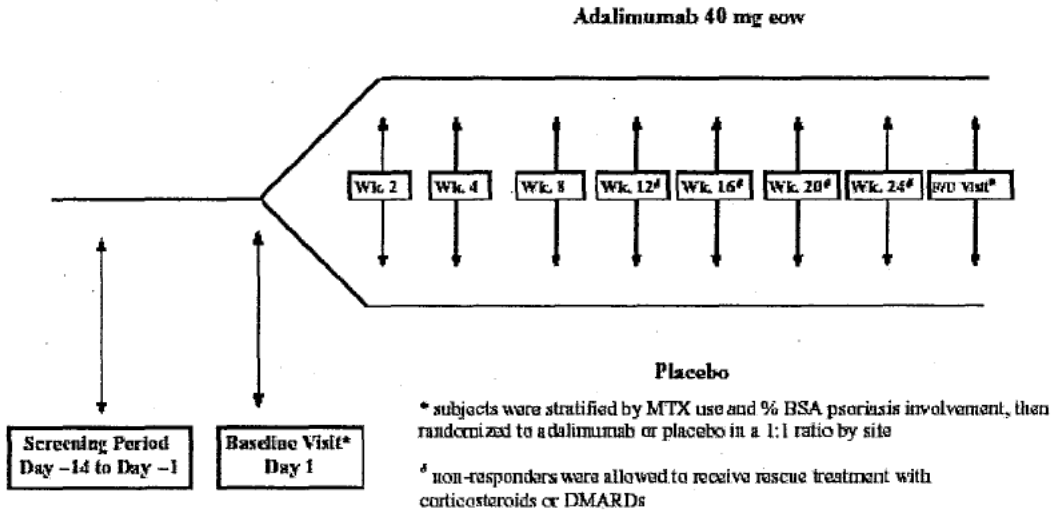
Adalimumab's effectiveness as a treatment for PsA was evaluated by the sponsor in two clinical efficacy trials, Studies M02-518 and M02-570, which were similar in design. These trials were multicenter, double-blind, placebo controlled, parallel group studies in patients with moderate to severe polyarticular PsA comparing 40 mg of adalimumab administered SC eow to placebo injections. This section will provide a full description of the pivotal trial Study M02-518 and describe also differences in the design of Study M02-570.

Study M02-518 was a 24-week, Phase III trial conducted at 50 sites in which 313 patients with active PsA on concomitant MTX therapy and suboptimal response to treatment with NSAIDs were randomized by site in 4-subject blocks via a 1:1 ratio stratified by concurrent MTX use and extent of psoriatic skin involvement ($\geq$ 3% and <3% BSA) to the following 2 treatment groups:

- adalimumab 40 mg SC eow
- placebo injection SC eow

At the Week 12 visit, patients who had demonstrated $\leq$20% improvement from baseline in both the swollen and tender joint counts documented on 2 consecutive assessments 4 weeks apart were eligible for early escape. The latter permitted subjects with active disease to receive adjustment of or initiation of corticosteroids or DMARDs while continuing their blinded study medications. Figure 1 is a schematic of the overall trial design and scheduled study visits and assessments:

Figure 1: Schematic Design of Study M02-518:



Patients who completed this study were eligible to participate in an open-label extension (OLE) study (Study M02-537) designed to assess the long-term safety and efficacy of adalimumab over approximately 120 weeks. Subjects who opted not to participate in the OLE trial were monitored for adverse events via a follow-up telephone call from their site investigator approximately 70 days after completing the study.

Study M02-570 was a 12-week, Phase III trial in 101 patients with active PsA from 20 sites that differed from Study M02-537 in that subjects could either be receiving treatment with concomitant DMARDs to which they had a suboptimal response or no background therapy. Like Study M02-518, this study also employed a 1:1 randomization ratio but it was stratified solely for concurrent DMARD use (yes, no). Its schedule of visits (e.g., screening visit, baseline visit, and study visits for Weeks 2, 4, 8 and 12) was identical to the trial schematic shown above in Figure 1. Due to this study's shorter duration, escape criteria were not included in its design. Completers of this study were also permitted to enroll in the on-going OLE trial, Study M02-537.

Eligibility:
In addition to having an inadequate response or intolerance to current or previous DMARD or NSAID therapy, study candidates for these 2 trials had to be 18 years in age or older, and in generally good health with active PsA. Table 3 summarizes the major inclusion and exclusion criteria for Studies M02-518 and 570:

Table 3 – Tabular Summary of Major Inclusion and Exclusion Criteria for Studies M02-570 and 518

	Study	
Inclusion Criteria	**M02-570**	**M02-518**
Diagnosis of PsA of moderate to severe activity as defined by ≥3 swollen joints and ≥3 tender or painful joints	X	X
Concurrent DMARD therapy of history of DMARD therapy with inadequate response as defined by the investigator	X	
Inadequate response or intolerance to NSAID therapy as defined by the investigator		X
Dose of oral corticosteroids not to exceed prednisone equivalent of ≤ 10 mg/day that must be stable for at least 4 weeks prior to baseline visit.	X	X
Subjects on MTX therapy must be have received a minimum of 3 months of therapy and had to be on a stable dose of ≤ 30 mg/week for at least 4 weeks prior to baseline visit	X	
Subjects on MTX or DMARD therapy (except cyclosporine or tacrolimus) had have received a minimum of 3 months of therapy and had to be on a stable dose for at least 4 weeks prior to baseline visit. Subjects on MTX must be on a dose ≤ 30 mg/week		X
Must have active cutaneous lesions of chronic plaque psoriasis or documented history of chronic plaque psoriasis diagnosed by the investigator or dermatologist	X	X
Exclusion Criteria		
Female subjects who are breast feeding, pregnant, not surgically sterile or are unwilling to practice a protocol approved method of contraception	X	X
Subjects who had received alefacept or siplizumab within 12 weeks prior to baseline; or any other biologic or investigational agent within 6 weeks prior to baseline	X	X
Subjects who had received prior therapy with other anti-TNF agents	X	X
Subjects who had received cyclosporine, tacrolimus or DMARDs (other than MTX) within 4 weeks prior to baseline		X
Subjects who had received cyclosporine or tacrolimus within 4 weeks prior to baseline	X	
Subjects who had received an intra-articular injection or intravenous infusion of corticosteroids within 4 weeks of baseline.	X	X
Subjects who had received topical psoriasis therapy (e.g., keratolytics, coal tar, antralin, etc.) within 2 weeks of baseline with the exception of the following: medicated shampoos and low potency topical steroids to be used for palms, soles of feet, axilla and groin area	X	X
Subjects who had received systemic psoriasis therapy (e.g., oral retinoids) within 4 weeks prior to baseline	X	X
Subjects who had received Ultraviolet A (UVA) phototherapy, including Psoralen plus Ultraviolet A (PUVA) or had used a tanning booth within 2 weeks prior to baseline	X	X
Subjects taking or likely to begin anti-retroviral therapy during the course of the trial	X	X
Subjects with a history of malignancy other than carcinoma in situ of the cervix or adequately treated, non-metastatic squamous or basal cell skin carcinoma	X	X

Concomitant Medications:

Both protocols allowed subjects to continue taking stable doses of background NSAIDs, oral corticosteroids (i.e., doses of ≤ 10 mg/day of prednisone or equivalent) and/or MTX ≤ 30 mg/week for the duration of the studies. Additionally, patients participating in Study M02-518 could also continue receiving stable doses of DMARDs other than MTX. Although the use of over-the-counter (OTC) and prescription analgesics was permitted provided their use was documented in patients' case report forms (CRF), patients were instructed not to use these drugs within 24 hours of a study visit. Local or intra-articular (IA) injections of corticosteroids were prohibited during the course of Study M02-570 and during the first 12 weeks of Study M02-518.

Patients enrolled in the latter study were permitted to receive up to 3 IA corticosteroid injections during Weeks 13-24 of the study. Any injected joint was subsequently excluded from future joint exams that occurred within a 28-day period following the injection.

Endpoints:
The primary endpoint for both studies was the proportion of patients who had achieved an ACR 20 response at Week 12. Study M02-518 additionally had a co-primary end point that assessed adalimumab's ability to inhibit the progression of structural joint damage in both hand and feet x-rays as measured by the mTSS at Week 24. These two co-primary endpoints were assessed in a sequential manner to preserve alpha.

Analyses were based on a modified intent-to-treat (ITT) population comprising those who received at least one dose of study drug and had at least one post-treatment efficacy assessment. The Cochran Mantel Haenszel test adjusted for MTX use and extent of psoriasis with non-responder imputation for missing data was used to calculate the primary endpoint in the pivotal study, M02-518. Although this same test was used to analyze the primary endpoint in the second trial, Study M02-570, a different stratification scheme was used that controlled only for baseline DMARD use.

Both protocols included assessment of numerous secondary and ancillary endpoints. A full listing of these ancillary endpoints is shown in Table 4. The statistical analysis plans for these studies prespecified that some of the secondary endpoints were to be calculated in a fixed order procedure. Those endpoints affected by this ranking are marked by an asterisk in Table 4.

Table 4 – Efficacy Variables

Efficacy Variable	Study	
	M02-570	M02-518
Arthritic Manifestations		
ACR20 Response	X	X
ACR50 and ACR70 Response*,**	X	X
Time to First ACR20, ACR50 and ACR70 Response	X	X
Tender Joint Count (TJC)	X	X
Swollen Joint Count (SJC)	X	X
Patient's Assessment of Pain	X	X
Patient's Global Assessment of Disease Activity	X	X
Physician's Global Assessment of Disease Activity	X	X
C-Reactive Protein (CRP)	X	X
Modified Psoriatic Arthritis Response Criteria (PsARC)	X	X
Dactylitis/Enthesitis	X	X
Structural Damage		
Change in Modified Total Sharp Scores on X-rays of Hands and Feet		X
Change in Modified Sharp Score Components*		X
Proportion of Subjects with No Change in Modified Total Sharp Score		X
Change in PsA-Specific Radiographic Scores		X
Disability		
Disability Index of the Health Assessment Questionnaire (HAQ)*,**	X	X
Skin Manifestations		
Psoriasis Area and Severity Index (PASI) 50 and 75*,**		X
Target Lesion Assessment**	X	
Physician's Global Assessment for Psoriasis*,**	X	X
Quality of Life		
Short Form Health Status Survey 36 (SF-36)	X	X
Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue	X	X
Dermatology Life Quality Index (DLQI)	X	X

*Designated as ranked secondary endpoints in Study M02-518
**Designated as ranked secondary endpoints in Study M02-570

6.1.4 Efficacy Findings

Patient Disposition:

A tabular summary of subjects' disposition from Studies 2-518 and 570 is shown in Table 5:

Table 5 – Subject Disposition for Studies M02-518 and 570

	Study M02-518		M02-570	
	Placebo	**Adalimumab**	**Placebo**	**Adalimumab**
Number of Patients Randomized	**162 (100%)**	**153 (100%)**	**51 (100%)**	**51 (100%)**
Number of Patients Treated	**162 (100%)**	**151 (99%)**	**49 (96%)**	**51 (100%)**
Number of Patients That Completed Week 12 Study Visit	**155 (96%)**	**144 (95%)**	**46 (90%)**	**50 (98%)**
Number of Patients That Completed Week 24 Study Visit	**149 (92%)**	**140 (93%)**	**N/A**	**N/A**
Number of Patients Withdrawn Prematurely Before Week 12:	**N/A**	**N/A**	**3 (6%)**	**1 (2%)**
Adverse Event			1 (2%)	1 (2%)
Lack of Efficacy			1 (2%)	0
Protocol Violation			1 (2%)	0
Number of Patients Withdrawn Prematurely Before Week 24:	**13 (8%)**	**11 (7%)**	**N/A**	**N/A**
Adverse Event	1 (1%)	3 (2%)		
Abnormal Lab Value	0	2 (1%)		
Lack of Efficacy	4 (3%)	1 (1%)		
Withdrew Consent	5 (3%)	3 (2%)		
Lost to Follow-Up	1 (1%)	0		
Protocol Violation	1 (1%)	0		
Administrative Problems	0	1 (1%)		
Other	1 (1%)	1 (1%)		
Number of Patients With Both Baseline and Week 24 X-Rays	**152 (94%)**	**144 (95%)**	**N/A**	**N/A**

The rates for subjects completing both studies were high with 92% and 90% of the patients randomized to Studies M02-518 and 570 respectively, finishing the studies. In Study M02-518, the percentage of patients who dropped out from either treatment group prior to the Week 24 time point was approximately the same (8% for placebo group versus 7% for adalimumab). Further examination of the data in Table 4 shows that slightly more patients from the placebo group in this trial dropped out prematurely due to lack of efficacy (3 subjects) and withdrawing of consent (5 subjects) as compared to the adalimumab group (1 patient and 3 patients, respectively). Slightly more subjects randomized to adalimumab failed to complete the study due to adverse events (3 patients versus 1 patient in the placebo group). Additionally, the percentage of patients in this study who had both sets of baseline and Week 24 x-rays completed was very high with 94% of the placebo group versus 95% in the adalimumab group accomplishing this task.

In the second study, Study M02-570, a higher number of subjects (3, 6%) prematurely withdrew from the placebo group as compared to the adalimumab treatment group (1, 2%) for a variety of reasons as listed in Table 4: adverse event (1 patient, 2%), lack of efficacy (1 patient, 2%) and protocol violation (1 patient, 2%). (Refer to Table 5.)

Primary Analyses:

The primary efficacy parameter for both controlled studies was the percentage of patients with an ACR 20 response at Week 12. In the pivotal trial, Study M02-518, 58% of patients treated with adalimumab versus 14% of the placebo treated patients achieved an ACR 20 response at Week 12 ($p < 0.001$). The results generated from the stratified analysis of this co-primary efficacy endpoint that used a non-responder imputation technique for missing study data are shown in Table 6 below. A higher proportion of responders was observed in the adalimumab group whether patients had concomitant MTX or not and irrespective of whether they had higher or lower extent of psoriasis.

Table 6 – First Co-Primary Psoriatic Arthritis Endpoint: ACR20 Response at Week 12 (Full Analysis Set) for Study M02-518

ACR20 Response	**Placebo eow (N=162)**				**Adalimumab 40 mg eow (N=151)**			
MTX Use at Baseline	**Yes (N=81)**		**No (N=81)**		**Yes (N=77)**		**No (N=74)**	
Extent of Psoriasis, (%BSA)	≥3% (N=28)	<3% (N=53)	≥3% (N=42)	<3% (N=39)	≥3% (N=29)	<3% (N=48)	≥3% (N=41)	<3% (N=33)
Week 12: Responder, N (%)	**3 (11)**	**5 (9)**	**6 (14)**	**9 (23)**	**17 (59)**	**25 (52)**	**25 (61)**	**20 (61)**
Overall Stratum Response Rate:	**14%**				**58%**			
P-value[1]:	**p<0.001**							

Note: BSA= body surface area; MTX=methotrexate
[1]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use and extent of psoriasis (≥ 3% BSA, <3% BSA) as the stratification factors and nonresponder imputation technique for missing data.

Study M02-570 also met its primary endpoint, although the treatment effect (Table 7) was less (23% versus 44%) than that seen in Study M02-518. The stratified analysis of this study's primary efficacy endpoint which also employed the use of a non-responder analysis for missing data revealed that 39% of the adalimumab treated patients achieved an ACR 20 response at Week 12 as compared to 16% of the placebo treatment group (p=0.012).

Table 7– Primary Psoriatic Arthritis Endpoint: ACR20 Response at Week 12 (Full Analysis Set) for Study M02-570

ACR20 Response	Placebo eow (N=49)		Adalimumab 40 mg eow (N=51)	
DMARD Use at Baseline	Yes (N=33)	No (N=16)	Yes (N=35)	No (N=16)
Week 12: Responder, N (%)	6 (18%)	2 (13%)	14 (40%)	6 (38%)
Overall Stratum Response Rate:	16%		39%	
P-value[1]:	p=0.012			

[1]P-values based on CMH mean score test with baseline DMARD use as stratification factors. Missing responses were counted in the non-responder category for analysis

The following sensitivity analyses were conducted that further assessed the robustness of the outcomes from the primary efficacy analyses for both controlled studies including: imputation of the worst case and the modified worst case, a completers analysis, subjects' corrected MTX strata, and the evaluable patient population. In general, the results generated from these additional analyses (Table 8) are consistent with those from the studies' primary analyses of the ACR20 response at Week 12. These findings are not unexpected given the relatively small amount of missing data that occurred over the courses of Studies M02-518 and 570.

Table 8 – Sensitivity Analyses of the ACR20 at Week 12 for Studies M02-518 and 570

Week 12 ACR20	Study M02-518 (N=313)				Study M02-570 (N=100)			
	Placebo eow (n=162)		Adalimumab 40 mg eow (n=151)		Placebo eow (n=49)		Adalimumab 40 mg eow (n=51)	
	N	Response Rate	N	Response Rate	N	Response Rate	N	Response Rate
Imputing the Worst Case - Overall Stratum Rate:	162	15%	151	58%	49	16%	51	39%
P-value[1]	p<0.001				p=0.012			
Imputing Modified Worst Case Overall Stratum Rate:	162	14%	151	58%	49	16%	51	39%
P-value[1]	p<0.001				p=0.012			
Subjects Who Completed the Study Overall Stratum Rate:	149	15%	140	60%	46	17%	50	40%
P-value[1]	p<0.001				p=0.017			
Corrected MTX/DMARD Stratification Overall Stratum Rate:	162	14%	151	58%	49	16%	51	39%
P-value[1]	p<0.001				p=0.012			
Evaluable Subjects Overall Stratum Rate:	148	15%	131	58%	45	18%	48	40%
P-value[1]	p<0.001				p=0.022			

[1]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use and extent of psoriasis (≥ 3% BSA, <3% BSA) as the stratification factors and nonresponder imputation technique for missing data.

As mentioned in Section 6.1.3, Study M02-518 was designed to have a second co-primary endpoint, the change from baseline to Week 24 in mTSS. The statistical analysis plan for this study mandated that its co-primary efficacy variables were to be analyzed in a hierarchal manner.

Table 9 – Second Co-Primary Psoriatic Endpoint: Modified Total Sharp Score (mTSS) at Week 24 (Intent-to-Treat Population) and Component Scores Subanalyses for Erosions and Joint Space Narrowing for Study M02-518

Parameter at Week 24	Placebo eow n=162		Adalimumab 40mg eow n=151		P-Value[1]
	Baseline	Mean Change	Baseline	Mean Change	
mTSS[2,3]	19.0	1.6 ± 7.5	22.6	1.0 ± 8.6	p<0.001
Erosion Score[4]	9.9	0.7 ± 2.01	11.4	0.5 ± 4.60	p<0.001
Joint Space Narrowing Score[5]	9.1	0.6 ± 2.66	10.9	0.1 ± 3.72	p<0.001

[1]P-value for differences between treatment groups from a ranked ANCOVA with treatment group and Baseline MTX use/extent of psoriasis (≥3% BSA, <3% BSA) as factors and ranked baseline modified total Sharp score as the covariate.
[2]mTSS ranged from 0-570 and included the joint space narrowing score (48 sites [0-4 for each site]for a range of 0-192) plus erosion score (54 sites [0-7 for each site] for a range of 0-3780. A lower score indicates a better result.
[3]Values were imputed for subjects with missing change values
[4]Erosion Score: 54 sites (0-7 for each site) for a range of 0-378. A lower score indicates a better result.
[5]Joint Space Narrowing Score: 48 sites (0-4 for each site) for a range of 0-192. A lower score indicates a better result.

As shown in Table 9 for the ITT population, patients in the adalimumab group had significantly (p<0.001) less progression on their x-rays compared to placebo treated patients as measured by the mTSS. The validity of this finding is supported by the results generated from the mTSS component subanalyses for erosion and joint space narrowing scores which are also listed in the above Table 9. The results from these comparative subanalyses of the study's ITT population are consistent with that of the mTSS (p<0.001 for each of the subanalyses). The sponsor employed the following pre-specified imputation technique for missing data from a total of 17 patients (10 from the placebo group and 7 from the adalimumab group) that did not have complete sets of baseline and Week 24 x-rays necessary to calculate the mTSS, or the erosion and joint space narrowing scores shown in the Table 9:

- For subjects missing Week 24 films: an imputed value was used that was generated from the calculation of the 75th percentile within pre-specified strata based on baseline MTX use and mTSS at baseline
- For subjects missing both the baseline and Week 24 films: imputated values used were calculated from the change in the 75th percentile from baseline and the median of the baseline values within pre-specified strata based on baseline MTX use
- For subjects missing baseline films: no imputated value was generated since all subjects had their baseline films

The above ITT analysis of radiographic progression is a conservative analysis that minimizes bias from missing data. Additional explorations of Study M02-518's x-ray data were conducted that included only patients who had both baseline and Week 24 films.

Table 10 - Modified Total Sharp Score (mTSS), Erosion and Joint Space Narrowing Scores at Week 24 in Subjects with X-rays at Both Baseline and Week 24 for Study M02-518

Parameter at 24 Weeks	Placebo eow n=152		Adalimumab 40mg eow N=144		P-Value[1]
	Baseline	Mean Change	Baseline	Mean Change	
mTSS[2,3]	20.0	1.0 ± 2.99	22.3	-0.2 ± 1.39	p<0.001
Erosion Score[4]	10.5	0.6 ±2.03	11.4	0.0 ± 0.62	p<0.001
Joint Space Narrowing Score[5]	9.5	0.4 ±1.62	10.9	-0.2 ±1.10	p<0.001

[1]P-value for differences between treatment groups from a ranked ANCOVA with treatment group and Baseline MTX use/extent of psoriasis (≥3% BSA, <3% BSA) as factors and ranked baseline modified total Sharp score as the covariate.
[2]mTSS ranged from 0-570 and included the joint space narrowing score (48 sites [0-4 for each site] for a range of 0-192) plus erosion score (54 sites [0-7 for each site] for a range of 0-3780. A lower score indicates a better result.
[3]Subjects with missing change values were excluded from the analysis.
[4]Erosion Score: 54 sites (0-7 for each site) for a range of 0-378. A lower score indicates a better result.
[5]Joint Space Narrowing Score: 48 sites (0-4 for each site) for a range of 0-192. A lower score indicates a better result.

As shown in Table 10, adalimumab treated patients who had both baseline and Week 24 films also had significantly less progression in their x-rays as compared to the placebo group as measured by the mTSS, as well as on their erosion and joint space narrowing scores ($p< 0.001$ for all three comparative analyses). Thus, these additional x-ray analyses support the robustness of the findings from the ITT population based analyses of the co-primary endpoint for Study M02-518.

An additional analysis was undertaken to examine the proportion of subjects experiencing any radiographic progression (Table 11). A higher percentage of placebo-treated patients (32%; 51/162) experienced radiographic progression as shown by an increase in their mTSS than adalimumab treated patients (12%; 18/151).

Table 11 – Tabular Summary of Subjects with No Change in Modified Total Sharp Score at Week 24 (Full Analysis Set) for Study M02-518

Modified Total Sharp Score Change at Week 24[1]	Placebo eow n=162		Adalimumab 40mg eow n=151		P-Value[1]
	n	(%)	n	(%)	
Decrease	8	5%	28	19%	<0.001
No Change	103	63%	105	70%	
Increase	51	32%	18	12%	

[1]Decrease is < -0.5 change from baseline; No change is –0.5 to 0.5 change; Increase is >0.5 change from Baseline.
[2]P-value based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use and extent of psoriasis (≥ 3% BSA, <3% BSA) as the stratification factors. This tests for a difference between treatment groups in the distribution across the 3 categories (i.e., decrease, no change, increase).

Despite the paucity of missing x-ray data, a variety of sensitivity analyses of the mTSS at Week 24 for Study M02-518 were conducted as follows: imputating values from the 50th percentiles or

a zero change from baseline, the actual change from baseline, re-reads of x-rays, completer analysis, and subjects' corrected MTX strata. The results generated from these sensitivity analyses are listed in Table 12:

Table 12 – Sensitivity Analyses of Modified Total Sharp Score at Week 24 for Study M02-518

Modified Total Sharp Score	Placebo eow n=162			Adalimumab 40mg eow n=151			P-Value[1]
	N	Mean	Median	N	Mean	Median	
Imputing the 50th Percentiles							
Baseline	162	19	--	151	23	--	
Change at Wk 24	162	1.1	0.0	151	-0.3	0.0	<0.001
Using Actual Change From Baseline							
Baseline	162	19	--	151	23	--	
Change at Wk 24	162	1.6	0.0	151	1.0	0.0	0.457
Using Re-Reads							
Baseline	162	19	--	151	23	--	
Change at Wk 24	162	1.6	0.0	151	1.0	0.0	<0.001
Imputing a Zero Change From Baseline							
Baseline	162	19	--	151	23	--	
Change at Wk 24	162	1.0	0.0	151	-0.2	0.0	<0.001
Subjects Who Completed the Study							
Baseline	149	20	--	140	22	--	
Change at Wk 24	149	1.0	0.0	140	0.2	0.0	<0.001
Subjects With Corrected MTX Strata							
Baseline	162	19	--	151	23	--	
Change at Wk 24	162	1.6	0.0	151	1.0	0.0	<0.001

Review of the data summarized in Table 12 shows that the results generated from these sensitivity analyses are consistent with the results from the primary analyses of this endpoint with the exception of the calculation which used the actual change from baseline (p=0.457). The results of the latter are not surprising in view of the fact that the actual modified Sharp scores were non-normally distributed and this analysis utilized actual scores from the ANCOVA analysis instead of ranked data.

To assess the generalizability of the radiographic findings subgroup analyses of the mTSS at Week 24 were carried out based on baseline characteristics (Table 13). The small numbers of patients in some of the subgroups such as non-Caucasians, patients with spondylitis, DIP arthropathy and arthritis mutilans variants of disease precluded the formulation of meaningful conclusions. In addition, since the placebo-treated patients with asymmetric oligoarthritis had almost no radiographic progression it is impossible to judge the effects of adalimumab damage in this subset. This finding is not unexpected since patients with asymmetric oligoarthritis

subvariant have milder disease and their baseline mTSS scores are very low. The findings from the other subgroup analyses are consistent with the results from the primary analyses.

Table 13 – Modified Total Sharp Scores at Week 24 by Subgroup (Full Analysis Set) for Study M02-518

Week 24 mTSS	Placebo eow (N=162)			Adalimumab 40 mg eow (N=151)		
	N	Baseline	Mean Change	N	Baseline	Mean Change
Age (quartiles)						
20-41 years	29	8.4	0.6	36	11	-0.3
41-50 years	41	30	1.8	40	18	0.0
50-56 years	40	17	0.5	33	15	-0.1
56-88 years	42	21	1.2	35	45	-0.2
Sex						
Male	84	14	0.6	81	17	0.0
Female	68	27	1.6	63	30	0.0
Race						
Caucasian	143	20	0.9	140	23	-0.2
Non-Caucasian	9	23	2.8	4	12	0.3
Psoriatic Arthritis Subtype:						
Symmetric Polyarthritis	105	26	1.4	92	27	-0.2
Asymmetric Oligoarthritis	39	5	0.1	35	7.0	-0.1
DIP Arthropathy	7	12	0.6	15	12	-0.2
Spondylitis	1	2	3.5	1	3.0	0.0
Arthritis Mutilans	0	--	--	1	348	0.0
Baseline MTX Use						
Yes	78	25	1.2	76	22	-0.3
No	74	15	0.9	68	23	-0.1
Rheumatoid Factor						
Positive	14	21	1.0	15	42	-0.1
Negative	137	19	1.0	129	20	-0.2
Duration of PsA (quartiles)						
0-3.2 years	38	10	1.1	36	9.0	-0.2
3.2-7.5 years	45	17	1.4	29	12	-0.1
7.5- 13.2 years	31	27	0.6	43	27	0.0
13.2- 52.8 years	38	27	1.0	36	38	-0.3
Body Weight						
45.4 -73.0 kg	34	30	1.6	35	40	-0.3
73 - 85.0 kg	40	15	0.5	34	24	0.0
85.0 - 96.9 kg	39	14	0.9	39	17	0.3
96.6 - 156.0 kg	38	23	1.4	36	10	-0.6

[1]P-values for differences between treatment groups from a ranked ANCOVA with treatment group as the factor and ranked baseline mTSS as the covariate.
[2] Note: N/A denotes that a statistical comparison was not performed as there were <5 subjects in one treatment group.

Secondary and Ancillary Endpoints:

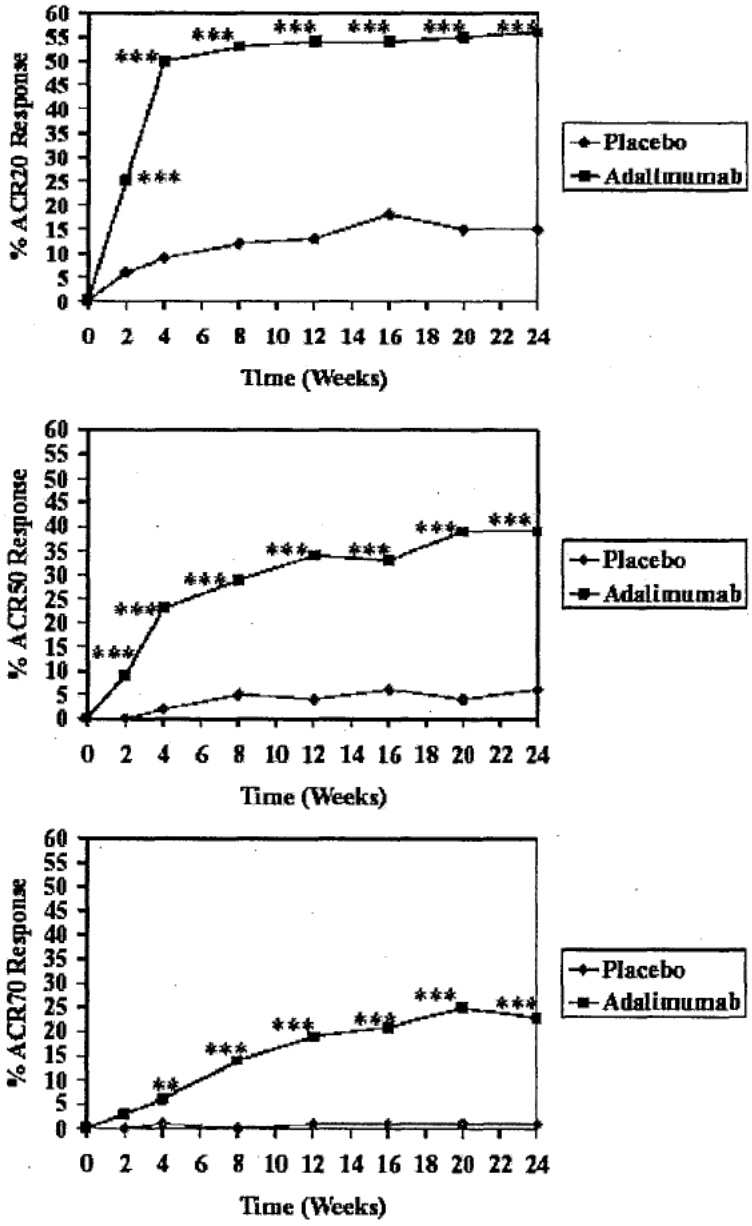
Both studies included a large number of secondary and ancillary endpoints for assessment as noted in Section 6.1.2. The results of secondary variables that evaluated x-ray manifestations of PsA were discussed above with their corresponding co-primary endpoint, the mTSS. The outcomes of the remaining secondary ancillary parameters will be presented in this section based on the disease-related domains they evaluated as follows: arthritic manifestations, disability, skin manifestations, and quality of life.

Arthritic Manifestations:

The arthritic manifestations of patients' PsA were evaluated by the ACR 50 and 70 responses at Week 12 in both studies, and by the ACR 20, 50 and 70 responses at Week 24 in the pivotal trial, Study M02-518. The time courses of the ACR 20, 50 and 70 responses for the treatment groups in the latter study are shown in Figures 1A, B, and C. Responses to adalimumab were observed in some patients as early as Week 12. A greater proportion of adalimumab treated patients achieved ACR 50 and 70 responses than in the placebo group. Statistically significant differences between treatment groups appeared as early as Week 2 for both the ACR 20 and 50 scores ($p=0.001$), and by Week 4 for the ACR 70 score ($p=0.002$). Responses to adalimumab therapy were seen at Week 12 for each parameter, and were maintained out to Week 24.

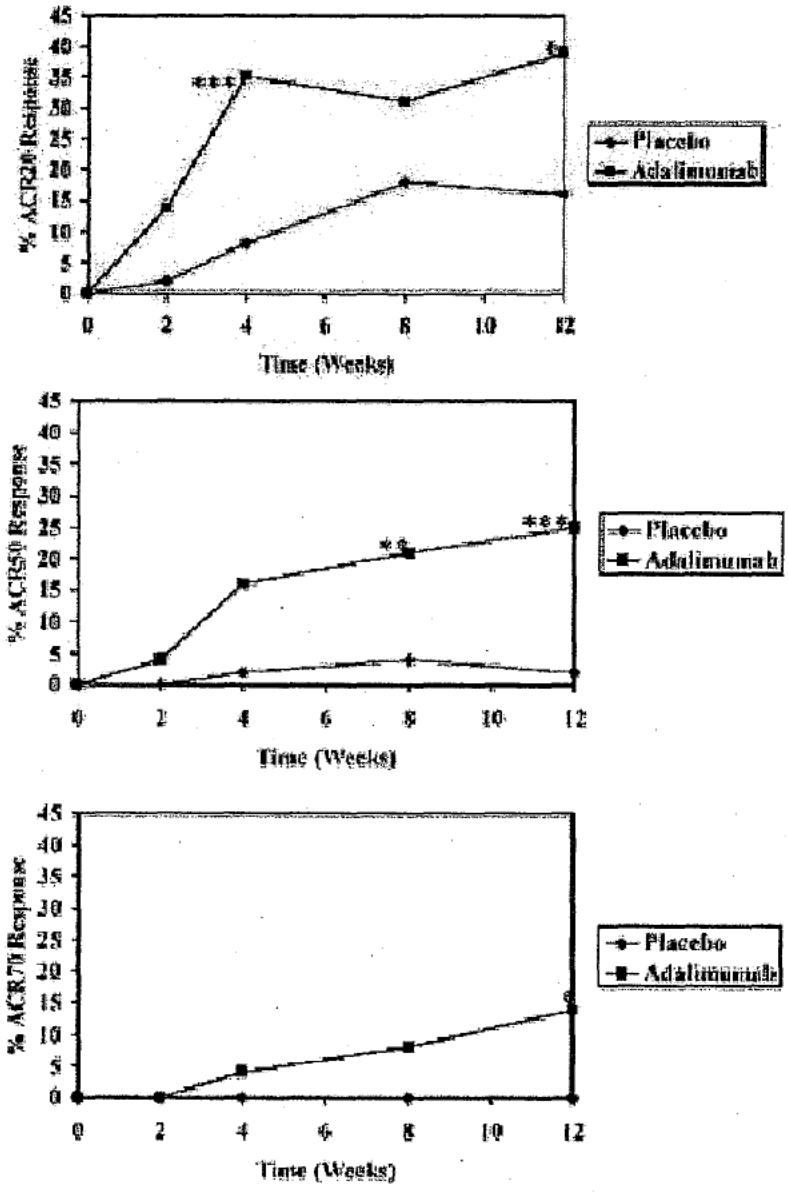
Figures 2A, B and C, depict the time course of the ACR 20, 50 and 70 responses for the second controlled trial, Study M02-570. Although a higher rate of ACR 20 response to adalimumab was seen as early as Week 2 it did not achieve statistical significance until Week 4. A statistically significant increase in ACR 50 and ACR 70 responses was also observed. Although a higher percentage of patients from the adalimumab treatment group achieved ACR 20, 50 and 70 responses as compared to placebo, the point estimates were lower than in Study M02-518. A tabular summary of the ACR responses from the two studies is provided in Table 14.

Figures 1A, B, C – Time Course of ACR20, ACR50, and ACR70 Responses by Treatment Group for Study M02-518



Note: *, ** Statistically significant at p=0.001 and 0.002 levels, respectively**
Non-responder imputation technique used for missing data

Figures 2A, B, C, - Time Course of the ACR20, ACR50, and ACR70 Responses by Treatment Group for Study M02-570



Note: *, **, * Statistically significant at p=0.001, p=0.01 and p=0.05 levels, respectively versus placebo.**
Nonresponder imputation technique used for missing data

The results from the analyses of the psoriatic arthritic response criteria (PsARC) evaluations for both studies are also shown in Table 14.

Table 14 – Time Course of ACR 20, 50, 70 and Modified Psoriatic Arthritic Response Criteria (PsARC) Responses at Weeks 12 and 24 for Study M02-518 and Week 12 for Study M02-570

Joint Manifestations	Study M02-518 (N=313)			Study M02-570 (N=100)		
	Placebo eow (N=162)	Adalimumab 40 mg eow (N=151)	P-Value[1]	Placebo eow (n=49)	Adalimumab 40 mg eow (n=51)	P-Value[2]
	Response Rate	Response Rate		Response Rate	Response Rate	
ACR20 -						
Week 12:	14%	58%	p<0.001	16%	39%	p=0.012
Week 24:	15%	57%	p<0.001	--	--	
ACR50 -						
Week 12:	4%	36%	p<0.001	2%	25%	p<0.001
Week 24:	6%	39%	p<0.001	--	--	
ACR70 -						
Week 12:	1%	20%	p<0.001	0%	14%	p=0.013
Week 24:	1%	23%	p<0.001	--	--	
PsARC[3] -						
Week 12:	26%	62%	p<0.001	24%	51%	p=0.007
Week 24:	23%	60%	p<0.001	--	--	

[1]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use and extent of psoriasis (≥ 3% BSA, <3% BSA) as the stratification factors and nonresponder imputation technique for missing data.
[2]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline DMARD use as the stratification factor.
[3]PsARC – Worsening of criteria is defined as ≥ 20% increase in global assessments or ≥ 30% increase in joint counts.

As discussed in Section 6.1.2, the PsARC is a validated assessment tool commonly used in PsA studies. In Study M02-518, 62% at Week 12 and 60% at Week 24 of the patients treated with adalimumab had improvements in their PsARC score as compared to 26% and 23% of the placebo group respectively (p<0.001 for both Weeks 12 and 24). Similar results were seen in Study M02-570 where 51% of the adalimumab treatment group met criteria for disease improvement as measured by the PsARC versus 24% of the placebo group (p=0.007 at Week 12). As shown in Table 14, the point estimate for the magnitude of the PsARC response was higher at 12 Weeks (62%) for the adalimumab-treated patients in the pivotal trial, Study M02-518, than in Study M02-570 (51%). The improvement in PsARC was maintained out to the Week 24 timepoint.

To explore the generalizability of the effects of adalimumab on signs and symptoms, we examined subgroup analyses of the Week 12 ACR 20 responses for Study M02-518. A higher response rate to adalimumab compared to placebo was seen for patients subsetted by age, gender, race, PsA subtypes, duration of PsA, and body weight. A few subgroups (uncommon PsA subtypes and RF negative patients) had too few patients to draw conclusions (Table 15).

Table 15 – Tabular Summary of ACR20 Response at Week 12 by Subgroups (Full Analysis Set) for Study M02-518

Observed Week 12 ACR20 Response	Study M02-518 (N=313)		
	Placebo eow (n=162)	Adalimumab 40 mg eow (n=151)	P-value[1]
Age			
20-41 years	36 (11%)	42 (79%)	<0.001
41-50 years	39 (18%)	36 (58%)	<0.001
50-56 years	43 (14%)	33 (58%)	<0.001
56-88 years	44 (14%)	40 (35%)	0.039
Sex			
Male	89 (13%)	86 (58%)	<0.001
Female	73 (15%)	66 (58%)	<0.001
Race			
Caucasian	152 (14%)	147 (58%)	<0.001
Non-Caucasian	10 (10%)	4 (50%)	N/A[2]
Psoriatic Arthritis Subtype:			
Symmetric Polyarthritis	113 (15%)	97 (56%)	<0.001
Asymmetric Oligoarthritis	40 (10%)	37 (62%)	<0.001
DIP Arthropathy	8 (25%)	15 (60%)	0.193
Spondylitis	1 N/A	1 N/A	N/A[2]
Arthritis Mutilans	0 N/A	0 N/A	N/A[2]
Baseline MTX Use			
Yes	81 (10%)	77 (55%)	<0.001
No	81 (19%)	74 (61%)	<0.001
Rheumatoid Factor			
Positive	15 (7%)	16 (25%)	0.333
Negative	146 (15%)	135 (61%)	<0.001
Duration of PsA			
0-3.2 years	41 (10%)	38 (63%)	<0.001
3.2-7.5 years	48 (15%)	28 (64%)	<0.001
7.5- 13.2 years	32 (13%)	48 (56%)	<0.001
13.2- 52.8 years	41 (20%)	37 (49%)	0.008
Body Weight			
45.4 -73.0 kg	36 (8%)	37 (59%)	<0.001
73 - 85.0 kg	42 (10%)	37 (65%)	<0.001
85.0 - 96.9 kg	43 (21%)	39 (56%)	<0.001
96.6 - 156.0 kg	40 (18%)	38 (50%)	0.004

[1]The p-values were based on Fisher's Exact test. Missing responses were counted in the non-responder category for analysis.
[2] Note: N/A denotes that a statistical comparison was not performed as there were <5 subjects in one treatment group.

To determine whether the results in the composite ACR index were broad or were limited to a subset of ACR components we examined the outcomes of the individual components of the ACR composite score (Table 16). Adalimumab-treated patients from Study M02-518 had significantly higher rates of improvement compared to the placebo group as measured by each of the 7 individual core ACR response index components ($p<0.001$) at both Weeks 12 and 24. Included in these core responses was the HAQ-DI which assesses disease related physical function. The improvement in the Week 12 HAQ-DI score for the adalimumab group (0.5 units) was significantly greater than for the placebo group score (0.0) ($p<0.001$) and this difference between

treatment arms was maintained until Week 24 of the study (adalimumab improvement -0.6 versus 0.0 score for the placebo group; $p<0.001$). Similar results were seen in Study M02-518.

Table 16 - Tabular Summary of ACR Component Responses at Weeks 12 and 24 (Last Observation Carried Forward) for Studies M02-518 and 570

ACR Component Responses	Study M02-518 (N=313)			Study M02-570 (N=100)		
	Placebo eow (n=162)	Adalimumab 40 mg eow (n=151)	P-value[1]	Placebo eow (n=49)	Adalimumab 40 mg eow (n=51)	P-value[2]
Tender Joint Count (0-78)						
Baseline	23	20		25	19	
Week 12	18	5.0		17	7.0	
% Change at Week 12	-14	-68	<0.001	-30	-60	0.041
Week 24	17	5.0		--	--	
% Change at Week 24	-10	-68	<0.001			
Swollen Joint Count (0-76)						
Baseline	11	11		15	17	
Week 12	10	4.0		13	8	
% Change at Week 12	-11	-60	<0.001	-17	-44	0.020
Week 24	9.0	3.0		--	--	
% Change at Week 24	-20	-67	<0.001	--		
Disability Index of the HAQ						
Baseline	1.0	1.0		1.1	1.0	
Week 12	1.0	0.5		0.9	0.4	
% Change at Week 12	-6.3	-48	<0.001	-11	-50	0.008
Week 24	1.0	0.4		--	--	
% Change at Week 24	-7.0	-50	<0.001			
Patient's Assessment of Pain (100 mm VAS)						
Baseline	49	54		51	42	
Week 12	49	22		54	22	
% Change at Week 12	3.4	-22	<0.001	-3.0	-38	0.001
Week 24	49	20		--	--	
% Change at Week 24	4.5	-51	<0.001			
Patient's Global Assessment of Disease Activity (100 mm VAS)						
Baseline	50	48		48	45	
Week 12	49	21	<0.001	47	24	
% Change at Week 12	0	-43		1.8	-39	0.002
Week 24	49	20	<0.001	--	--	
% Change at Week 24	4.0	-52				
Physician's Global Assessment of Disease Activity (100 mm VAS)						
Baseline	53	55		56	53	
Week 12	46	20		49	29	
% Change at Week 12	-17	-61	<0.001	-19	-42	0.002
Week 24	49	16		--	--	
% Change at Week 24	-9.0	-68	<0.001			
CRP (mg/dL)						
Baseline	0.8	0.8		0.9	0.7	
Week 12	0.7	0.2		0.9	0.1	
% Change at Week 12	2.0	-71	<0.001	-0.4	-64	<0.01
Week 24	0.7	0.2		--	--	
% Change at Week 24	-7.7	-66	<0.001			

[1]P-value for differences between treatment groups via Wilcoxon test.
[2]P-value for differences between treatment groups via Wilcoxon test.

Dactylitis and enthesitis are selective features of PsA that are not features of RA. The patients in Studies M02-518 and M02-570 had active dactylitis and enthesopathy at baseline. Dactylitis scores fell at 12 and 24 Weeks in both treatment groups. Although the dactylitis scores fell more in the adalimumab groups than in the control groups, the differences were not statistically significant (Table 17). There are no statistically significant differences between study arms in enthesopathy.

Table 17 – Tabular Summary of Dactylitis and Enthesitis Evaluations (LOCF) at Weeks 12 and 24 for Studies M02-518 and 570

	Study M02-518 (N=313)			Study M02-570 (N=100)		
	Placebo eow (n=162)	Adalimumab 40 mg eow (n=151)	P-value[1]	Placebo eow (n=49)	Adalimumab 40 mg eow (n=51)	P-value[2]
Dactylitis[3]						
Mean Baseline	2.1	2.3		2.5	2.9	
Week 12 Mean Change	-0.8	-1.5	0.185	-1.4	-2.4	0.242
Week 24 Mean Change	-1.1	-1.8	0.223	--	--	
Enthesopathy[4]						
Mean Baseline	0.9	0.8		1.0	0.9	
Week 12 Mean Change	0.1	-0.2	0.021	-0.2	-0.5	0.148
Week 24 Mean Change	-0.1	-0.2	0.247	--	--	

[1]P-value for differences between treatment groups from an ANOVA model with treatment group and Baseline MTX use/extent of psoriasis (≥3% BSA, <3% BSA) as factors.
[2]P-value for differences between treatment groups from a two-way ANOVA model with treatment group and baseline DMARD use as factors.
[3]Dactylitis: Possible total score of 0-60 with a 0 (absent) to 3 (severe) rating of each digit.
[4]Enthesitis: Possible total score of 0-4 with 0 (absent) or 1 (present) rating for proximal insertion of Achilles tendon and insertion of plantar fascia of each foot.

Disability:

The reader is referred to Table 16 and the corresponding narrative discussion located above for the results of the HAQ-DI evaluations for both studies.

Skin Manifestations:

A number of assessment tools were utilized in both studies to evaluate psoriatic skin lesion response to study therapy. Study M02-570 assessed target lesions in the subset of patients with plaque lesions at baseline. Both studies also evaluated the physician's global assessment for psoriasis. Study M02-518 also evaluated improvement in psoriasis based on the PASI 50 and 75. Both the physician's global assessment for psoriasis and the PASI evaluated the prespecified subset of patients with ≥ 3% body surface area (BSA) involvement of psoriasis at baseline. Table 18 shows that the 32 patients with plaque lesions at baseline who received adalimumab therapy in Study M02-570 had a mean change of -3.7 units in their target lesion assessment scores which

represents a significant improvement as compared to the mean change of -0.3 units experienced by the 29 placebo treated patients with target lesions at baseline.

Table 18 – Tabular Summary of Change Over Baseline Scores for Target Lesion Assessment (LOCF) at Week 12 for Study M02-570

Week 12 Time Point	Placebo eow (n=29)		Adalimumab 40 mg eow (N=32)		P-Value[1]
	Baseline	Mean Change	Baseline	Mean Change	
Target Lesion Assessment[2]	8.1	-0.3	7.9	-3.7	<0.001[1]

[1]P-value for differences between treatment groups from two-way ANOVA model with treatment group and baseline DMARD use as factors
[2]Possible range for a total target lesion score is 0-15 units (possible range of 0-5 for erythema, induration, and scaling) with a higher score indication a greater severity.

The results from the PASI 50 and 75 score evaluations using the last observation carried forward (LOCF) for missing data for Study M02-518 are shown below in Tables 19 and 20, respectively. A total of 69 randomized patients from each treatment group qualified for inclusion in these subset analyses of skin involvement stratified for baseline MTX use. For the PASI 50, the overall stratum response rate for adalimumab treated patients was 72%, which was significantly higher than the corresponding 15% response rate for the placebo group at Week 12 (p<0.001). This significant difference in PASI 50 stratum response rates was maintained by both groups through the Week 24 time point (75% for the adalimumab group versus 12% for the placebo group; p<0.001).

Table 19 – Psoriasis Area and Severity Index 50 (PASI) (Full Analysis Set) for Study M02-518 (N=313)

PASI 50 Response	Placebo eow (n=69)		Adalimumab 40 mg eow (n=69)		P-value[1]
MTX Use at Baseline	Yes (N=28)	No (N=41)	Yes (N=29)	No (N=40)	
Week 12: Responder, N (%)	6 (21)	4 (10)	22 (76)	28 (70)	
Overall Stratum Response Rate:	15%		72%		p<0.001
MTX Use at Baseline	Yes (N=28)	No (N=41)	Yes (N=29)	No (N=40)	
Week 24: Responder, N (%)	2 (0.1))	6 (0.2)	25 (86)	27 (68)	
Overall Stratum Response Rate:	12%		75%		p<0.001

[1]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use as the stratification factor using a score of 1 for the responder category and a score of 0 for the non-responder category. Missing responses were counted in the non-responder category for analysis.

Similar results were seen for the PASI 75 overall stratum response rates at the Week 12 and 24 time points as shown in Table 20. In this subset analysis, adalimumab-treated patients had a significantly higher response rate of 49% as compared to 4% for the placebo group at Week 12 (p<0.001). The patients in the former group maintained their significantly higher response rate (59%) to the Week 24 time point compared to the placebo group (1%).

Table 21 – Psoriasis Area and Severity Index 75 (PASI) (Full Analysis Set) for Study M02-518 (N=313).

PASI 75 Response	Placebo eow (N=69)		Adalimumab 40 mg eow (N=69)		P-value[1]
MTX Use at Baseline	Yes (N=28)	No (N=41)	Yes (N=29)	No (N=40)	
Week 12: Responder, N (%)	1 (0.04)	2 (0.05)	17 (59)	17 (43)	
Overall Stratum Response Rate:	4%		49%		p<0.001
MTX Use at Baseline	Yes (N=28)	No (N=41)	Yes (N=29)	No (N=40)	
Week 24: Responder, N (%)	0 (0))	1 (0.02)	21 (72)	20 (50)	
Overall Stratum Response Rate:	1%		59%		p<0.001

[1]P-values based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use as the stratification factor using a score of 1 for the responder category and a score of 0 for the non-responder category. Missing responses were counted in the non-responder category for analysis.

The sponsor also evaluated large improvements in psoriasis based on PASI 90 responses. The overall stratum-adjusted PASI 90 response rates for the adalimumab treated group at Weeks 12 (30%) and 24 (42%) were also significantly higher then those of the placebo group (0 for both Week 12 and 24 response rates; p=0.001)) in Study M02-518.

Table 23 shows the results of the physician's global assessment for psoriasis as measured by a 100 mm visual analogue scale. In Study M02-518, 62% (41/66) of patients from the adalimumab group had clear or almost clear evaluations as compared to 3% (2/63) of the placebo treated patients (p<0.001). By Week 24, the response rates for both groups had improved to 71% (46/65) with clear or almost clear evaluations for the adalimumab group versus 12% (7/59) for the placebo group (p<0.001). The Week 12 subgroup analysis results for the second trial, Study M02-570, were similar to those of the pivotal study with a significantly higher physician's global assessment rate of 41% (13/32) of patients from the adalimumab group rated as having cleared or almost cleared skin lesions versus 7% (2/29) for the placebo treatment group (p=0.003).

Table 23 – Physician's Global Assessment for Psoriasis for Weeks 12 and 24 (Full Analysis Set) for Study M02-518 and for Week 12 for Study M02-570

Physician's Global Assessment	Study M02-518 (N=313)					Study M02-570 (N=100)				
	Placebo eow (n=162)		Adalimumab 40 mg eow (n=151)		P-value[1]	Placebo eow (n=49)		Adalimumab 40 mg eow (n=51)		P-value[2]
	Baseline	Wk 12	Baseline	Wk 12		Baseline	Wk 12	Baseline	Wk 12	
Number	63	63	66	66	p<0.001	29	29	32	32	p<0.001
Almost Clear	1 (2%)	2 (3%)	0	33 (50%)		0	2 (7%)	1 (3%)	8 (25%)	
Clear	0	0	0	8 (12%)		0	0	0	5 (16%)	
	Baseline	Wk 12	Baseline	Wk 12		Baseline	Wk 12	Baseline	Wk 12	
Number	59	59	65	65	p<0.001	N/A[3]		N/A		
Almost Clear	1 (2%)	7 (12%)	0	24 (37%)		N/A		N/A		
Clear	0	0	0	22 (34%)		N/A		N/A		

[1]Based on Cochran-Mantel-Haenszel mean score test with Baseline MTX use as the stratification factor.
[2]Based on Cochran-Mantel-Haenszel mean score test with Baseline DMARD use as the stratification factor.
[3]N/A: not applicable

Health-Related Quality of Life Assessments (HR-QOL):

Although the health-related quality of life (HR-QOL) assessment tools used in both studies were designated as ancillary study end points by their respective statistical analysis plans, the results from these assessments are included in this review for the purpose of completeness and because of their emerging importance in the field of clinical trial design. Three different HR-QOL parameters were included as part of the trial evaluations performed during Studies M02-518 and 570: the Dermatology Life Quality Index (DLQI), the SF-36 Health Status Survey, and the FACIT Fatigue Scale. The DLQI evaluated the HR-QOL of patients with $\geq$ 3% body surface area (BSA) involvement of psoriasis at study baseline. Table 22 summarizes the Week 12 DLQI results from both studies and the Week 24 DLQI results for Study M02-518. Mean baseline values of the DLQI were similar between treatment groups for both studies. The mean improvement from baseline in the DLQI for the adalimumab group was significantly higher than that of the placebo group for both Week 12 and 24 time points (adalimumab group: -6.1 versus placebo group: -0.3 at Week 12; adalimumab group: -6.4 versus placebo group: -0.5 at Week 24; p<0.001 for both comparisons). A significant improvement in the DLQI as measured at Week 12 was not seen in Study M02-570 (adalimumab group: -3.4 versus placebo group: -1.7 at Week 12; p=0.171).

Table 22 – Dermatology Life Quality Index [DLQI] (Full Analysis Set) for Studies M02-518 and 570

DLQI[1]	Study M02-518 (N=313)		Study M02-570 (N=100)	
	Placebo eow	Adalimumab 40 mg eow	Placebo eow	Adalimumab 40 mg eow
Number of Patients	**60**	**62**	**28**	**32**
Mean Baseline	**10**	**9.0**	**6**	**7.6**
Mean Change from Baseline at Week 12	**-0.3**	**-6.1**	**-1.7**	**-3.4**
P-value	P<0.001[2]		p=0.171[3]	
Number of Patients	**59**	**60**	--	--
Mean Baseline	**9.7**	**8.8**	--	--
Mean Change from Baseline at Week 24	**-0.5**	**-6.4**		
P-value	P<0.001[2]		N/A	

[1]Possible range for DLQI is 0-30 with a higher score indicating a more impaired quality of life.
[2]P-value for differences between treatment groups from an ANOVA model with treatment group and Baseline MTX use as factors.
[3]P-value for differences between treatment groups from two-way ANOVA model with treatment group and baseline DMARD use as factors

Since clinically meaningful improvements in PsA have not been defined for the SF-36 Health Status Survey, defined differences from the evaluation of RA patients are used as substitutes. Although all 10 domains of the SF-36 were assessed in Studies M02-518 and 570, only the results from the physical component and mental component summaries are presented below in Table 23. In the RA population, clinically meaningful improvements in the summary component scores in the SF-36 are demonstrated to be >2.5 point increase over baseline score. Clinically meaningful improvements in the physical component summary that were also statistically significant were seen in the adalimumab group as compared to the placebo group at both Weeks 12 (9.3 versus 1.4 respectively) and 24 (9.3 versus 1.5 respectively) in Study M02-518 ($p<0.001$), but no meaningful improvements were noted on the between group comparisons at Weeks 12 (1.6 versus 1.2) and 24 (1.9 versus 0.4) in this study for the mental component summary or for the comparative analyses of the physical summary (adalimumab: 5.7 versus placebo: 1.8) or mental summary (adalimumab: 1.1 versus -0.6) components at Week 12 in Study M02-570.

Table 23 – SF-36 Health Status Survey Domain Scores (Full Analysis Set) For Studies M02-518 and 570

SF-36[1] Domain Scores	Study M02-518 (N=313)			Study M02-570 (N=100)		
	Placebo eow (n=162)	Adalimumab 40 mg eow (n=151)	P-value[2]	Placebo eow (n=49)	Adalimumab 40 mg eow (n=51)	P-value[3]
Physical Component Summary						
Mean Baseline	33	33		32	35	0.082
Mean Change at Week 12	1.4	9.3	<0.001	1.8	5.7	
Mean Baseline	34	33		--	--	
Mean Change at Week 24	1.5	9.3	<0.001	--	--	
Mental Component Summary						
Mean Baseline	47	48		51	51	0.242
Mean Change at Week 12	1.2	1.6	0.708	-0.6	1.1	
Mean Baseline	47	48		--	--	
Mean Change at Week 24	0.4	1.9	0.203	--	--	

[1]SF-36: Total possible score of 0-100 with a higher score indicating a better health state
[2]P-value for differences between treatment groups from an ANOVA model with treatment group and Baseline MTX use/extent of psoriasis (≥3% BSA, <3% BSA) as factors.
[3]P-value for differences between treatment groups from two-way ANOVA model with treatment group and baseline DMARD use as factors.

As for the SF-36, clinically meaningful improvements in PsA have not been defined for the FACIT Fatigue score. Thus differences from the evaluation of RA patients are used as substitutes. In the RA population, studies have shown clinically meaningful improvements in the FACIT score as a 4-point change. Clinically meaningful improvements that were also statistically significant were seen in the adalimumab group as compared to the placebo group at both Weeks 12 (6.5 versus 0.6 respectively) and 24 (7.1 versus 0.2 respectively) in Study M02-518 ($p<0.001$), but no meaningful improvements were noted on the between group comparisons at Week 12 in Study M02-570 (2.6 for the adalimumab group versus 2.3 for the placebo group; $p=0.783$). (See Table 24).

Table 24 - FACIT Fatigue Scale Scores (Full Analysis Set) for Study M02-518

FACIT Fatigue Scale Scores[1]	Study M02-518 (N=313)		Study M02-570 (N=100)	
	Placebo eow (N=162)	Adalimumab 40 mg eow (N=151)	Placebo eow (n=49)	Adalimumab 40 mg eow (n=51)
Mean Baseline	**31**	**31**	**31**	**35**
Mean Change from Baseline at Week 12	**0.6**	**6.5**	**2.3**	**2.6**
P-value	p<0.001[2]		p=0.783	
Mean Baseline	**31**	**31**	--	--
Mean Change from Baseline at Week 24	**0.2**	**7.1**	--	--
P-value	p<0.001[2]		N/A	

[1]FACIT score has range from 0-52 with a higher score indicating less fatigue
[2]P-value for differences between treatment groups from an ANOVA model with treatment group and Baseline MTX use/extent of psoriasis (≥3% BSA, <3% BSA) as factors.
[1]P-value for differences between treatment groups from two-way ANOVA model with treatment group and baseline DMARD use as factors.

6.1.6 Efficacy Conclusions

The efficacy of adalimumab in the treatment of active PsA was demonstrated by the successful results from two multicenter, double-blind, randomized, placebo-controlled trials, Studies M02-518 and 570. In the pivotal trial, Study M02-518, adalimumab was shown to effectively reduce signs and symptoms of active arthritis in patients with moderate to severe PsA with an inadequate response or intolerance to NSAID therapy as measured by a plethora of assessments. Positive outcomes were also seen for improvement in physical function, inhibiting the short-term progression of joint damage and improvement in health related quality of life. These results were supported by similar findings from the second trial, Study M02-570 in patients with moderate to severe PsA with an inadequate response or intolerance to DMARD therapy.

7 Integrated Review of Safety

7.1 Methods and Findings

7.1.1 Deaths

No deaths were observed during the conduct of Studies M02-518, 570 and 537.

7.1.2 Other Serious Adverse Events (SAEs)

Treatment–emergent AEs were defined by the sponsor as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug. Table 25 summarizes the treatment-emergent AEs that were reported in the safety database generated from Studies M02-518 and 570. Although the overall percentages of combined

patients who reported any AEs (80% versus 74%), any serious AE (4% versus 3%), any severe AE (7% versus 4%) and any infectious AEs (38% versus 38%) during the 2 controlled studies were similar for both the placebo and adalimumab groups, further examination of the individual trial safety data reveals that fewer adalimumab treated patients (53%) experienced AEs as compared to placebo-treated patients (80%) during the 12-week trial, Study M02-570. A higher percentage of placebo-treated patients in this study reported having AEs that were characterized by investigators as serious (4%), severe (8%) or infectious (33%) AEs than patients in the adalimumab group (2%, 4%, and 18% respectively). Additionally, equal numbers (7 subjects, 3%) of patients discontinued from the total combined treatment groups in this safety database due to AEs. There were no malignancies reported in either of these 2 trials.

Table 25 – Tabular Summary of Treatment-Emergent Adverse Events (AEs) Reported During the Controlled Studies M02-518 and M02-570

	Study M02-518		Study M02-570		Combined Total	
	Placebo (N=162)	Adalimumab 40 mg eow (N= 151)	Placebo (N=49)	Adalimumab 40 mg eow (N= 51)	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)
Any AE:	130 (80%)	122 (81%)	39 (80%)	27 (53%)	169 (80%)	149 (74%)
Any Serious AE:	7 (4%)	5 (3%)	2 (4%)	1 (2%)	9 (4%)	6 (3%)
Any Severe AE:	11 (7%)	5 (3%)	4 (8%)	2 (4%)	15 (7%)	7 (4%)
Any Infectious AE:	64 (40%)	68 (45%)	16 (33%)	9 (18%)	80 (38%)	77 (38%)
Any Serious Infectious AE:	1 (0.6%)	1 (0.7%)	1 (2%)	0	2 (1%)	1 (1%)
Any Malignancies:	0	0	0	0	0	0
Discontinuations Due to AEs:	5 (3%)	6 (4%)	2 (4%)	1 (2%)	7 (3%)	7 (3%)
Deaths:	0	0	0	0	0	0

Note: Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug.
Subjects may be counted in more than one AE parameter.

Long-term safety data in support of this application was generated by the ongoing OLE trial, Study M02-537. Table 26 summarizes the treatment-emergent AEs observed in the evaluable patient population from all 3 study populations combined.

Table 26 – Tabular Summary of the Number (%) of Subjects Who Experienced Treatment-Emergent Adverse Events (AEs) From Safety Database Generated by All Psoriatic Arthritis Studies

Treatment-Emergent Adverse Event[1,2]	Adalimumab 40 mg eow (N=395)
Any Adverse Event	293 (74%)
Any Serious Adverse Event	17 (4%)
Any Severe Adverse Event	22 (6%)
Any Infectious Adverse Event	161 (41%)
Any Serious Infectious Adverse Event	2 (1%)
Any Malignancies (including Lymphoma)[3]	2 (1%)
Discontinuations Due to Adverse Events	14 (4%)
Deaths	0

[1]Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of adalimumab was administered to 70 days after the last dose of adalimumab.
[2]Subjects may be counted in more than one AE parameter.
[3]Excluding non-melanoma skin cancers.

Minor increases in the overall percentages of AEs reported in the combined evaluable patient database as compared to the controlled studies are noted in the above table. Additionally, there were 2 malignancies reported during the OLE study. A more detailed discussion of the safety data generated from these 2 controlled trials and the OLE study will be presented in the following sections.

During the two controlled studies, a total of 15 AEs that were characterized by investigators as being serious in nature were reported by 9 placebo treated patients versus 6 SAEs by patients treated with adalimumab (Table 25 shown above). An additional 12 SAEs associated with the use of adalimumab were reported by 11 patients in the ongoing OLE trial, Study M02-537 that occurred prior to the Week 24 visit cut-off date of 5/17/04 (refer to preceding Table 26). (Note: One patient from the OLE study reported having 2 SAEs.) Table 27 is a tabular profile of all of the treatment emergent SAEs by treatment group for all PsA studies included in this submission.

Table 27 – Number (%) of Subjects with Treatment-Emergent Serious Adverse Events (SAEs) by Treatment Groups for All Psoriatic Arthritis Studies

Adverse Event	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Any Serious Adverse Event	**9 (4%)**	**6 (3%)**	**17 (4%)**
Cardiac Disorders:	**2 (1%)**	**0**	**1 (0.3%)**
CAD Aggravated	1 (0.5%)	0	0
Myocardial Infarction	0	0	1 (0.3%)
Pericarditis NOS	1 (0.6%)	0	0
Congenital, Familial and Genetic Disorders:	**0**	**0**	**1 (0.3%)**
Diverticulitis Meckel's	0	0	1 (0.3%)
Gastrointestinal Disorders:	**0**	**1 (0.5%)**	**2 (0.5%)**
Diverticulosis	0	1 (0.5%)	1 (0.3%)
Pancreatitis	0	0	1 (0.3%)
Hepatobiliary Disorders:	**0**	**0**	**1 (0.3%)**
Cholelithiasis	0	0	1 (0.3%)
Immune System Disorders:	**0**	**0**	**1 (0.3%)**
Amyloidosis	0	0	1 (0.3%)
Infections:	**2 (1%)**	**1 (0.5%)**	**2 (0.5%)**
Cellulitis	1 (0.5%)	0	0
Gastroenteritis	0	0	1 (0.3%)
Meningitis Viral	0	1 (0.5%)	1 (0.3%)
Oral Infection	1 (0.5%)	0	0
Injury:	**1 (0.5%)**	**0**	**0**
Hand Fracture	1 (0.5%)	0	0
Metabolism/Nutrition	**1 (0.5%)**	**0**	**0**
Hyperglycemia	1 (0.5%)	0	0
Musculoskeletal Disorders:	**1 (0.5%)**	**0**	**2 (0.5%)**
Muscle Weakness Aggravated	1 (0.5%)	0	0
Rhabomyolysis	0	0	1 (0.3%)
Spondylolisthesis	0	0	1 (0.3%)
Neoplasms Benign:	**0**	**1 (0.5%)**	**3 (0.8%)**
Non-Hodgkin's Lymphoma	0	0	1 (0.3%)
Paraganglion Neoplasm benign	0	1 (0.5%)	1 (0.3%)
Prostate Cancer	0	0	1 (0.3%)
Nervous System Disorders:	**0**	**1 (0.5%)**	**1 (0.3%)**
Convulsions Aggravated	0	1 (0.5%)	1 (0.3%)
Psychiatric Disorders:	**1 (0.5%)**	**0**	**0**
Depression	1 (0.5%)	0	0
Renal/Urinary Disorders:	**0**	**1 (0.5%)**	**2 (0.5%)**
Calculus Renal	0	1 (0.5%)	1 (0.3%)
Renal Failure	0	0	1 (0.3%)
Respiratory Disorders:	**0**	**1 (0.5%)**	**1 (0.3%)**
Nasal Septum Disorder	0	1 (0.5%)	1 (0.3%)
Surgical Procedures:	**0**	**1 (0.5%)**	**1 (0.3%)**
Toe Arthrodesis	0	1 (0.5%)	1 (0.3%)
Vascular Disorders:	**3 (1.4%)**	**0**	**1 (0.3%)**
CVA	1 (0.5%)	0	0
Pulmonary Embolism	1 (0.5%)	0	1 (0.3%)
Venous Thrombosis Deep Limb	1 (0.5%)	0	0

Note: Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug. Subjects may be counted in more than one AE parameter.

As shown in Table 27, the overall frequency of SAEs among adalimumab treated subjects was not higher than in placebo-treated patients in the PsA study database and was less then 5%. The profile of SAEs reported during the placebo-controlled portions of the 2 PsA studies and during the ongoing OLE are similar to what has been observed in previous clinical trials of adalimumab. A summary of all of these SAE cases is presented in Table 28.

Table 28 – Tabular Summary of Patients with Treatment-Emergent Serious Adverse Events from All Psoriatic Arthritis Studies

Sex/Age	Study Onset Day	Resolved	Serious Adverse Event	Significant History
Adalimumab Treated Subjects:				
49 yo/M	Day 96	Yes	Nasal Septum Disorder	None
40 yo/F	Day 57	Yes	Toe Arthrodesis	Elective arthrodesis of 3 toes on left foot
36 yo/M	Day 159	Yes	Convulsions Aggravated	H/O seizures, valproic acid and carbamazepine
42 yo/F	Day 85	Yes	Meningitis Viral	None
49 yo/M	Day 49	Yes	Calculus Renal	None
47 yo/F	Day 52	Yes	Diverticulitis	H/O MTX and diverticulosis; failed oral antibiotics for flare of diverticulosis
55yo/F	Day 47	Yes	Myocardial Infarction	H/O HTN and Hyperlipidemia
27yo/F	Day 64	Yes	Cholelithiasis	H/O oral contraceptives
40yo/M	Day 40	Yes	Gastroenteritis	None.
56yo/M	Day 71	Ongoing	Amyloidosis	H/O chronic diarrhea, anemia and renal insufficiency
65yo/F	Day 46	Ongoing	Pulmonary embolism	None
49yo/F	Day 226	Yes	Diverticulitis Meckel's	Congenital. Resected without sequalae.
49yo/F	Day 207	Yes	Spondylolisthesis	L5-S1 disease. Surgically fused.
64yo/M	Day 83	Ongoing	Prostate Ca	Dx. on routine biopsy
79yo/M	Day 4	Ongoing	NHL	H/O DM, weight loss and fatigue for 1 yr.
59yo/F	Day 114	Yes	Pancreatitis	H/O sulfasalazine
30yo/M	Day 30	Ongoing	Renal Failure; Rhabdomyolysis	H/O cholesterol lowering agents (simvastatin), analgesic and opiate abuse
Placebo Treated Subjects:				
50 yo/F	Day 60	Yes	Cerebrovascular Accident	None
44 yo/M	Day 96 Day 150	Yes Ongoing	Pericarditis; Hand Fracture	None. Fx due to accident
52 yo/M	Day 111 Day 114 Day 118	Ongoing Ongoing Ongoing	Muscle Weakness Aggravated; Pulmonary Embolism; Venous Thrombosis Deep	H/O muscle weakness of LEs; Negative neuro W/U. PE and DVT occurred during hospitalization
34 yo/M	Day 113	Yes	Depression	H/O depression
52 yo/F	Day 18 Day 37	Yes Yes	Hypoglycemia; Hypoglycemia	H/O diabetes mellitus and metformin; switched to insulin
73 yo/M	Day 102	Yes	Cellulitis (RLE)	Treated with oral antibiotic
48 yo/M	Day 36	Yes	Coronary Artery Disease Aggravated	H/O CAHD, HTN, and DM; S/P cardiac stent
68 yo/F	Day 62	Yes	Oral Infection Secondary to Calcified Sublingual Foreign Body	H/O dental infection; oral corticosteroids. Failed course of oral antibiotics. Admitted for IV antibiotics.
37 yo/F	Day 69	Yes	Paraganglion Neoplasm Benign	Presented with right neck mass; successfully resected

7.1.2.1 Malignancies

The currently approved label for adalimumab contains a warning about malignancies including lymphomas. Although no malignancies were observed during the controlled studies, two malignancies were reported during the OLE, Study M02-570 (Table 29). One case involved a 64 year old male who developed prostate cancer. The other case was a 79 year old male who developed NHL after 1 dose of adalimumab. Further examination of the latter case revealed that this patient was a diabetic and had been experiencing weight loss and fatigue for over a year prior to study entry. Signs consistent with early disease were noted on retrospective review of his radiographic studies.

Table 29 – Subjects Reporting Treatment-Emergent Malignancies (Safety Analysis Set)

Subject Number	Age/Sex	Rx Onset Day[1]	Malignancy	Severity	Causality
Study M02-537					
570-0953[2]	64yo/M	Day 83	Prostate Cancer	Mild	Probably Unrelated
570-1205[2]	79yo/M	Day 4	Non-Hodgkin's Lymphoma	Moderate	Probably Unrelated

7.1.2.2 Infections

A total of 4 serious infections were observed during these 3 studies which are listed in Table 30. Two of these cases (1 case of cellulitis and 1 case of oral infection secondary to a foreign body) were reported by patients randomized to placebo treatment during the controlled studies. The third case occurred in an adalimumab patient who developed viral meningitis that necessitated the subject's premature withdrawal from Study M02-518. The last serious infection in the safety database occurred in the OLE study, and involved a patient who developed severe gastroenteritis that resulted in the subject's hospitalization. No sequalae were associated with any of these cases.

Table 30 – Number (%) of Subjects Experiencing Treatment-Emergent Serious Infectious Adverse Events by Treatment Groups for the Combined Controlled Studies

	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Any Serious Infectious AE	2 (1%)	1 (0.5%)	2 (0.5%)
Cellulitis	1 (0.5%)	0	0
Gastroenteritis	0	0	1 (0.3%)
Meningitis Viral Nos	0	1 (0.5%)	1 (0.3%)
Oral Infection	1 (0.5%)	0	0

Note: The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports 2 or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 21 patients in the application's safety database prematurely withdrew from further study participation due to the development of a study related AE. (See Tables 25 and 26 above.) Seven of the 21 patients who discontinued due to AEs were patients treated with placebo. The remaining 14 cases involved patients treated with adalimumab, 7 of whom dropped out during the placebo-controlled portions of Studies M02-518 and 570 while the remaining 7 patients dropped out during the ongoing OLE trial.

7.1.3.2 Adverse events associated with dropouts

Table 31 lists by treatment group all patients who prematurely withdrew by their trial-related organ class AE. An equal number of patients (7 subjects, 3%) discontinued from both treatment groups during the double-blind portion of the 2 studies due to AEs. Adalimumab patients stopped study therapy due to a variety of events including idiopathic thrombocytopenic purpura (1 subject; 0.5%), diverticulosis (1 subject; 0.5%), pancreatitis (1 subject; 0.5%), viral meningitis (1 subject; 0.5%), abnormal liver function tests (1 subject; 0.5%), and anxiety disorder (1 subject; 0.5%). None of the AEs leading to premature withdrawal of a patient from the OLE were experienced by more than 1 patient. The AE profile leading to termination of study therapy in the OLE study was similar to that seen in the controlled studies.

Table 31 – Number (%) of Subjects Who Prematurely Withdrew due to Adverse Events for Safety Analysis Set

Adverse Event[2] System Organ Class	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Adalimumab 40 mg eow (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Any Discontinuations Due to Adverse Events:	7 (3%)	7 (3%)	14 (3%)
Blood and Lymphatic System Disorders:			
Idiopathic Thrombocytopenic	0	1 (0.5%)	1 (0.3%)
Purpura	0	1 (0.5%)	1 (0.3%)
Gastrointestinal Disorders:	0	2 (1%)	2 (0.5%)
Diverticulitis NOS	0	1 (0.5%)	1 (0.3%)
Pancreatitis acute	0	1 (0.5%)	1 (0.3%)
General/Administ. Disorders:	1 (0.5%)	0	0
Injection Site Reaction	1 (0.5%)	0	0
Infections:	0	1 (0.5%)	2 (0.5%)
Fungal Infection NOS	0	0	1 (0.3%)
Meningitis viral NOS	0	1 (0.5%)	1 (0.3%)
Investigations	0	1 (0.5%)	1 (0.3%)
Liver Function Test NOS Abnormal	0	1 (0.5%)	1 (0.3%)
Musculoskeletal and Connective Tissue Disorders:	4 (2%)	0	2 (0.5%)
Psoriatic Arthropathy Aggravated	4 (2%)	0	1 (0.3%)
Rhabdomyolysis	0	0	1 (0.3%)
Neoplasms Benign, Malignant and Unspecified:	0	0	2 (0.5%)
Non-Hodgkin's Lymphoma NOS	0	0	1 (0.3%)
Prostate Cancer	0	0	1 (0.3%)
Psychiatric Disorder:	0	1 (0.5%)	2 (0.5%)
Anxiety NOS	0	1 (0.5%)	1 (0.3%)
Depression Aggravated	0	0	1 (0.3%)
Renal and Urinary Disorders:	0	0	1 (0.3%)
Renal Failure NOS	0	0	1 (0.3%)
Skin and Subcutaneous Tissue Disorders:	3 (1.4%)	0	2 (0.5%)
Psoriasis	3 (1.4%)	0	1 (0.3%)
Rash NOS	0	0	1 (0.3%)

[1]Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of adalimumab was administered to 70 days after the last dose of adalimumab. Only AEs occurring in at least 3% of subjects are present.
[2]More than one AE category per subject possible.

7.1.3.3 Other Significant Adverse Events

Severity of AEs was assessed as mild, moderate, or severe by the study investigators. A total of 22 patients treated with adalimumab in this safety database experienced AEs that were classified as severe in nature by study investigators. Table 32 lists all of the treatment-emergent severe

AEs by treatment group organ class for all of the PsA studies. Diverticulosis, which occurred in two adalimumab-treated subjects, was the only severe AE reported to have occurred more than once.

Table 32 – Number (%) of Subjects with Treatment-Emergent Severe Adverse Events Occurring in Treatment Groups For All Psoriatic Arthritis Studies

Adverse Event	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Any Severe AE	**15 (7%)**	**7 (4%)**	**22 (6%)**
Cardiac Disorders:	**0**	**0**	**1 (0.3%)**
Myocardial Infarction	0	0	1 (0.3%)
Congenital, Familial and Genetic Disorders:	**0**	**0**	**1 (0.3%)**
Diverticulitis Meckel's	0	0	1 (0.3%)
Gastrointestinal Disorders:	**1 (0.5%)**	**2 (1%)**	**3 (0.8%)**
Diarrhea	1 (0.5%)	0	1 (0.3%)
Diverticulosis	0	2 (1%)	2 (0.5%)
Gen. Disorders/Administration Site Conditions:	**1 (0.5%)**	**0**	**3 (0.8%)**
Influenza-Like Illness	0	0	1 (0.3%)
Edema Lower Limb	0	0	1 (0.3%)
Pain	1 (0.5%)	0	1 (0.3%)
Hepatobiliary Disorders:	**0**	**0**	**1 (0.3%)**
Cholelithiasis	0	0	1 (0.3%)
Immune System Disorders:	**0**	**0**	**1 (0.3%)**
Amyloidosis	0	0	1 (0.3%)
Infections and Infestations:	**4 (2%)**	**2 (1%)**	**2 (0.5%)**
Bronchitis	1 (0.5%)	0	0
Influenza	1 (0.5%)	0	0
Meningitis Viral	0	1 (0.5%)	1 (0.3%)
Oral Infection	1 (0.5%)	0	0
Tooth Abscess	1 (0.5%)	0	0
URT Infection	0	1 (0.5%)	1 (0.3%)
Injury, Poisoning and Procedural Complications:	**0**	**0**	**1 (0.3%)**
Post-Procedural Pain	0	0	1 (0.3%)
Metabolism/Nutritional Disorders:	**1 (0.5%)**	**0**	**0**
Hypoglycemia	1 (0.5%)	0	0
Musculoskeletal/Connective Tissue Disorders:	**4 (2%)**	**1 (0.5%)**	**6 (1.5%)**
Arthralgia	0	0	1 (0.3%)
Back Pain	0	1 (0.5%)	1 (0.3%)
Intervertebral Disc Herniation	0	0	1 (0.3%)
Joint Destruction	0	0	1 (0.3%)
Muscle Weakness Aggravated	1 (0.5%)	0	0
Neck Pain	1 (0.5%)	0	0
Psoriatic Arth. Aggravated	2 (1%)	0	1 (0.3%)
Rhabomyolysis	0	0	1 (0.3%)
Nervous System Disorders:	**1 (0.5%)**	**0**	**0**
Migraine Aggravated	1 (0.5%)	0	0
Psychiatric Disorders:	**1 (0.5%)**	**0**	**0**
Depression	1 (0.5%)	0	0
Renal and Urinary Disorders:	**2 (1%)**	**0**	**1 (0.3%)**
Calculus Renal NOS	1 (0.5%)	0	0
Renal Colic	1 (0.5%)	0	0
Renal Failure	0	0	1 (0.3%)

Note: Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug. Subjects may be counted in more than one AE parameter.

Table 32 (cont.) - Number (%) of Subjects with Treatment-Emergent Severe Adverse Events Occurring in Treatment Groups For All Psoriatic Arthritis Studies

Adverse Event	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Skin and Subcutaneous Tissue Disorders:	**1 (0.5%)**	**1 (0.5%)**	**1 (0.3%)**
Psoriasis Aggravated	1 (0.5%)	1 (0.5%)	1 (0.3%)
Surgical and Medical Procedures:	**0**	**1 (0.5%)**	**1 (0.3%)**
Toe Arthrodesis	0	1 (0.5%)	1 (0.3%)
Vascular Disorders:	**1 (0.5%)**	**0**	**0**
Venous Thrombosis Deep	1 (0.5%)	0	0

Note: Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of study drug was administered to 70 days after the last dose of study drug. Subjects may be counted in more than one AE parameter.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Study personnel queried patients via open-ended questions to capture information regarding adverse event data during the course of these studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Treatment-emergent AEs in the PsA safety database were coded and tabulated via MedDRA body system classifications. The AE categorization and preferred terms were used appropriately by the sponsor in organizing this safety database.

7.1.5.3 Incidence of common adverse events

During the course of this review, the incidence of common adverse events was also examined. A detailed discussion can be found in Section 7.1.5.4.

7.1.5.4 Common adverse event tables

Table 33 summarizes the number and percentage of patients with treatment-emergent AEs that occurred in $\geq$ 3% of patients during the PsA studies. The percentage of patients experiencing any AE was not higher in the adalimumab group (74%) than in the placebo group (80%). The AEs most commonly reported by adalimumab-treated patients were: upper respiratory tract (URT) infections (52 subjects; 13%), nasopharyngitis (35 subjects; 9%), infection site reactions (25 subjects; 6%), headache (19 subjects; 5%) and herpes simplex (15 subjects; 4%). All of

(b) (4)

Table 33 – Number (%) of Subjects with Treatment-Emergent AEs Occurring in ≥ 3% of Subjects in the Safety Database for all Psoriatic Arthritis Studies

Adverse Event	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395)
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Any Adverse Event:	169 (80%)	149 (74%)	**293 (74%)**
Gastrointestinal Disorders:			
Nausea	9 (4%)	8 (4%)	**16 (4%)**
Gen. Disorders/Administration Site Conditions:			
Fatigue	0	0	**13 (3%)**
Injection Site Pain	8 (4%)	8 (4%)	**0**
Injection Site Reaction NOS	7 (3%)	12 (6%)	**25 (6%)**
Infections and Infestations:			
Herpes Simplex	3 (1%)	7 (4%)	**15 (4%)**
Nasopharyngitis	17 (8%)	17 (8%)	**35 (9%)**
Pharyngitis	0	0	**13 (3%)**
Sinusitis	0	0	**21 (5%)**
URT Infection NOS	28 (13%)	28 (13%)	**52 (13%)**
Investigations:			
Alanine Aminotransferase Inc.	0	6 (3%)	**0**
Liver Function Tests NOS Abn.	1 (0.5%)	8 (4%)	**0**
Musculoskeletal and Connective Tissue Disorders:			
Back Pain	8 (4%)	6 (3%)	**12 (3%)**
Psoriatic Arth. Aggravated	18 (9%)	6 (3%)	**0**
Nervous System Disorders			
Headache NOS	17 (8%)	9 (5%)	**19 (5%)**
Respiratory and Thoracic Disorders:			
Cough	0	0	**12 (3%)**
Vascular Disorders			
Hypertension NOS	5 (2%)	9 (5%)	**14 (4%)**

[1]Treatment-emergent AEs were defined as AEs that were reported from the time that the first dose of adalimumab was administered to 70 days after the last dose of adalimumab. Only AEs occurring in at least 3% of subjects are present.
[2]More than one AE category per subject is possible.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Figure 4 in Section 7.2.1 lists the lab testing that was performed as part of the safety monitoring of patients who participated in Studies M02-518 and 570. Patients enrolled in the OLE trial, Study M02-570, had lab tests drawn at Weeks 0, 2, 6 ,12, 18, 24, 36, 48, 60, 72, 88, 104, 120 and then every 16 weeks thereafter until study completion.

7.1.7.3 Standard analyses and explorations of laboratory data

All abnormal lab tests reported during the three PsA studies were graded using the National Cancer Institute's Common Toxicity Criteria. A tabular summary of grade 3 and 4 lab abnormalities of patients who participated in the 3 PsA studies is shown in Table 34. Overall, the number of grade 3 and 4 lab abnormalities observed during the controlled studies were similar between study arms. More adalimumab-treated patients in the controlled studies were observed having increased liver function tests as measured by elevated alanine aminotransferase [ALT] (5 subjects; 2%) and aspartate aminotransferase [AST] (5 subjects; 2%) as compared to placebo patients (elevated ALT: 2 subjects, 1%; and elevated AST: 1 subjects; 0.5%). The latter finding has not been reported in prior clinical trials with the product and is not mentioned in the product's current approved label. Please see Section 7.1.7.4 for additional analyses of elevated liver enzymes.

Table 34 – Tabular Summary of Grade 3 and 4 Laboratory Test Abnormalities by Treatment Group for All the Psoriatic Studies

Lab Parameter	Combined Total for Double-Blind Controlled Studies M02-518 and M02-570		Total Adalimumab (N=395
	Placebo (N=211)	Adalimumab 40 mg eow (N= 202)	
Serum Chemistries:			
ALT, increased	2 (1%)	5 (2%)	9 (3%)
AST, increased	1 (0.5%)	5 (2%)	6 (2%)
Cholesterol, increased	0	1 (0.5%)	2 (0.5%)
Creatinine, increased	0	0	1 (0.3%)
Glucose, increased	12 (6%)	13 (6%)	25 (6%)
Phosphate, decreased	8 (4%)	6 (3%)	17 (4%)
Uric Acid, increased	16 (8%)	6 (3%)	28 (7%)
Sodium, decreased	0	2 (1%)	4 (1%)
Triglycerides, increased	0	5 (2%)	6 (2%)
Cell Counts:			
Hemoglobulin	1 (0.5%)	0	1 (0.3%)
Lymphocytes	2 (1.0%)	1 (0.5%)	3 (0.8%)
Neutropenia	1 (0.5%)	0	1 (0.3%)

7.1.7.4 Additional analyses and explorations

Due to the potential safety signal raised by the higher percentage of adalimumab patients with elevated ALT and AST test results during the controlled studies in the PsA safety database, further examination of these cases was undertaken. This search revealed that a total of 9 patients exposed to adalimumab in the submission's safety database had experienced grade 3 (i.e., > 5.0 – 20.0 x ULN) or 4 (i.e., > 20.0 x ULN) liver function test (LFT) abnormalities, which are summarized in Table 35.

Table 35 – Tabular Summary of Evaluable Study Subjects with Grade 3 or 4 Abnormal Liver Function Tests

Subject Number	Age/Sex	Concomitant Medications	Alcohol Use	Adverse Event
Elevated ALT Only				
518-0221	29 yo/F	Sulfamethoxazole/Trimethoprim	Occasional	Obesity, IDDM, Nonalcoholic steatohepatitis (NASH)
518-1545	54 yo/F	MTX, NSAID, antidepressants	None	
518-3441	48 yo/F	MTX, NSAID, Premarin, Ciprofloxacin, Azithromycin	Former	
570-1903	30 yo/M	Simvastatin	Moderate	Renal Failure due to Rhabdomyolysis
Elevated AST Only				
518-6022	46 yo/F	NSAID, Atovaquone and Proguanil	Occasional	Rhabdomyolysis with elevated CPK due to excessive training
Elevated AST and ALT				
518-0424	73 yo/M	Lipitor and Isoniazid	Moderate	
518-0461	59 yo/F	Lipitor, MTX , NSAID	None	
518-0801	53 yo/F	MTX, NSAID, OPTIFAST program	None	Obesity; S/P stomach stapling
518-4341	33 yo/M	MTX, NSAID	None	

As shown in Table 35, each of the 9 patients were taking concomitant medications that are known to cause hepatotoxicity (i.e., MTX, NSAIDs, statin class of cholesterol lowering agents, antibiotics). Four cases (Subjects 518-0221, 570-1903, 518-6022, and 518-0424) were confounded further by the use of alcohol. The elevations in ALT and AST seen in 2 patients (Subjects 570-1903 and 518-6022) may also have been due to associated metabolic conditions (i.e., renal failure and rhabdomyolysis). The etiological cause for the abnormal LFTs was established in only case, Subject 518-0221, whose diagnosis of non-alcoholic steatohepatitis was subsequently confirmed via a liver sonogram. Hepatic necrosis secondary to adalimumab was seen in the RA safety database and is listed under the adverse events section of the currently approved product label.

7.1.10 Immunogenicity

Adalimumab's immunogenicity was not assessed during Studies M02-518 and 570. Patients who participated in the OLE trial, Study M02-537, had blood samples drawn at Weeks 0, 12, 24 and 48 to assess anti-adalimumab antibody production. The results of the immunogenicity testing will be submitted later with the final study report.

7.1.11 Human Carcinogenicity

The PsA safety database contained 2 cases of malignancy that occurred during the OLE study which are described in Section 7.1.5.5. The approved current label for adalimumab contains a warning about an increased risk for the development of malignancies particularly lymphomas based on a safety signal identified in the RA studies conducted with the product. Although no additional safety signal was noted related to human carcinogenicity in the PsA safety database reviewed, the duration of the 2 controlled studies and the limited data generated from the ongoing OLE study were not long enough to assess carcinogenicity.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.1 Study type and design/patient enumeration

Located in the preceding Section 4 is Table 1, which is a tabular summary of the 3 studies that comprise the safety database for this submission. A detailed description and discussion of the design of the two double-blind, placebo controlled trials, Studies M02-518 and 570, can be found in Section 6.1.3. The types of studies, design and enumeration were deemed adequate for review.

7.2.1.2 Demographics

Table 36 is a tabular summary of the baseline demographics of patients who participated in Studies M02-518 and 570:

Table 36 - Baseline Demographic Summary of Patients Participating in Studies M02-518 (N=313) and M02-570 (N=100)

Demographic and Disease Characteristics	Study M02-518 (N=313)		Study M02-570 (N=100)	
	Placebo (n=162)	Adalimumab (n=151)	Placebo (n=49	Adalimumab (n=51)
Mean Age [years]	49	49	48	50
Age Group [years](%):				
<40	31 (19)	36 (24)	14 (29)	9 (18)
40-64	119 (74)	104 (69)	32 (65)	38 (75)
65-74	11 (7)	5 (3)	1 (2)	4 (8)
≥75	1 (1)	6 (4)	2 (4)	0
Gender (%):				
Male	89 (55)	85 (56)	24 (49)	22 (43)
Female	73 (45)	66 (44)	25 (51)	29 (57)
Race (%):				
Caucasian	152 (94)	147 (97)	46 (94)	50 (98)
Black	2 (1)	1 (1)	0	0
Asian	5 (3)	0	0	0
American Indian/Alaskan	0	0	1 (2)	0
Other	3 (2)	3 (2)	2 (4)	1 (2)
Weight [kilograms] (Mean)	86	86	89	92

The patients who participated in these trials were overwhelmingly Caucasian as shown in Table 36.

Overall, the study populations enrolled in both studies were representative of patients with moderate to severe PsA as shown in the tabular summary of patients' disease characteristics (Table 37).

Table 37 - Summary of Patients' Disease Characteristics Who Participated in Studies M02-518 and 570

Demographic and Disease Characteristics	Study M02-518 (N=313)		Study M02-570 (N=100)	
	Placebo (n=162)	Adalimumab (n=151)	Placebo (n=162)	Adalimumab (n=151)
Randomized in the MTX-Using Stratum:			N/A	N/A
Yes	81 (50)	77 (51)		
No	81 (50)	74 (49)		
Randomized in the DMARD-Using Stratum:	N/A	N/A		
Yes			33 (67)	35 (69)
No			16 (33)	16 (31)
Number of Prior DMARDs (Mean)	1.5	1.5	2.1	1.7
Baseline Extent of Psoriasis:			N/A	N/A
≥3% BSA	70 (43)	70 (46)		
<3% BSA	92 (57)	81 (54)		
Duration of Psoriasis in Years (Mean)	17	17	14	18
Duration of Psoriatic Arthritis in Years (Mean)	9.2	9.8	7.0	8.0
Subtype of Psoriatic Arthritis:				
Symmetric Polyarthritis	113 (70)	97 (64)	41 (84)	42 (82)
Asymmetric Oligoarthritis	40 (25)	37 (25)	7 (14)	5 (10)
DIP Arthropathy	8 (5)	15 (10)	0	3 (6)
Spondylitis	1 (1)	1 (1)	1 (2)	1 (2)
Arthritis Mutilans	0	1 (1)	0	0
Spondylitis:				
Yes	24 (15)	29 (19)	10 (20)	10 (20)
No	138 (85)	122 (81)	39 (80)	41 (80)
Baseline Rheumatoid Factor:				
Negative	146 (90)	135 (89)	48 (98)	41 (80)
Positive	15 (9)	16 (11)	1 (2)	10 (20)
Concomitant Therapy During Study:				
Any DMARD	89 (55)	78 (52)	33 (67)	33 (65)
Corticosteroids	23 (14)	22 (15)	9 (19)	4 (8)
Any NSAID (including COX-2s)	123 (76)	111 (74)	44 (90)	37 (73)

7.2.1.3 Extent of exposure (dose/duration)

The duration of adalimumab exposure for all PsA studies in the safety database is shown in Table 38. The mean duration of adalimumab exposure was approximately 183 days. The dose of adalimumab evaluated in all 3 studies was 40 mg eow, but 24 patients who failed to respond by Week 12 of the OLE study were allowed to escalate dose to 40 mg weekly. Although the frequencies of AEs observed in patients exposed to the higher dosing regimen was similar to that

of patients exposed to 40 mg eow of adalimumab, no clinically meaningful conclusions can be made regarding the safety profile of the higher dosing regimen due to the small number of patients involved.

Table 38 – Duration of Adalimumab Exposure for All Psoriatic Arthritis Studies

	Duration of Treatment[1] N (%)
Any Exposure	**395 (100%)**
>4 Weeks	**385 (98%)**
>12 Weeks	**335 (85%)**
>24 Weeks	**185 (47%)**
>36 Weeks	**91 (23%)**
>48 Weeks	**1 (0.3%)**
>60 Weeks	**0**
Mean Duration of Treatment in Days[2]:	**183 Days**

[1]Duration of treatment = last dose date –first dose date +1
[2]Duration of treatment = last dose date –first dose date + 15

Patient's compliance with study medications was determined by counting the returned unused syringes and medications. As shown in Table 39, overall compliance with study medications was good for both studies with greater than 82% of the patients taking all of their study injections.

Table 39 - Subject Exposure to Study Medications During Studies M02-518 and M02-570

	Study M02-518		Study M02-570	
	Placebo (N=162)	Adalimumab (N=151)	Placebo (N=49)	Adalimumab (N=51)
Number of Patients That Received all Study Injections	133 (82%)	128 (85%)	40 (82%)	48 (94%)
Number of Patients Who Missed No More Than 5 of 6 Injections	N/A	N/A	46 (94%)	50 (98%)
Number of Patients Who Missed No More Than 11 of 12 Injections	147 (91%)	135 (89%)	N/A	N/A

7.2.3 Adequacy of Overall Clinical Experience

As shown in Table 40, a total of 395 patients from all 3 studies were included in the evaluable population for safety. Thirteen (13) patients who participated in the 2 controlled studies did not continue in the ongoing OLE study.

Table 40 – Subjects Included in Safety Database From All Psoriatic Arthritis Studies

	Adalimumab 40 mg eow (N=395)
Safety Analysis Set for All Studies[1,2]	**395**
Subjects Who Received Adalimumab in Study M02-537[3]:	**382**
Subjects Who Received Placebo in Study M02-570 or M02-518	193
Subjects Who Received Adalimumab in Study M02-570	51
Subjects Who Received Adalimumab in Study M02-518	138
Subjects Who Received Adalimumab in Study M02-570 or M02-518 but did not enter M02-537:	**13**
Subjects from Study M02-570	0
Subjects from Study M02-518	13

[1]Defined as all subjects who received at least one adalimumab injection in Study M02-570, M02-518, or M02-537.
[2]N may be smaller for analyses of some safety parameters.
[3]Subject 518-4801 received placebo in Study M02-518, then enrolled in Study M02-537 and never received adalimumab; therefore the total number of subjects who received adalimumab during Study M02-537 is 382 while the number enrolled is 383.

In view of the extensive safety experience with adalimumab in RA and the lack of new safety signals, the overall clinical experience is adequate to assess safety of adalimumab in PsA.

7.2.5 Adequacy of Routine Clinical Testing

A flowchart summarizing the safety assessments that were performed during scheduled clinic visits for Studies M02-518 and 570 is shown in Figure 4. These evaluations included medical history (Med. Hx), physical exam (PE), vital signs (VS) and weight, chest x-ray (CXR), electrocardiogram (EKG), lab testing, a PPD test, and monitoring of concomitant therapy and adverse events (AEs). The safety data collected from these safety evaluations has been discussed in the preceding sections of this review.

Figure 4 – Flowchart of Study Safety Assessments for Studies M02-518 and 570

Study Procedure	Screening Period	Study Periods										
	≤14 days prior to Baseline	Baseline	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16*	Wk 20*	Early Term[a]	Wk 24*	30 Days F/U Visit[b]	70 Days Post-Dose Visit[d]
Visits	X	X	X	X	X	X	X	X	X	X	X	
Med. Hx	X	X[c]										
PE	X	X	X	X	X	X	X	X	X	X	X	
VS/weight	X	X	X	X	X	X	X	X	X	X	X	
CXR	X											
X-rays of Hands/Feet		X*							X*	X*		
EKG	X											
Chemistry	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Testing	X											
PPD test	X											
Prior and Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment		X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug		X	X	X	X	X	X	X				
Collect unused study meds						X			X	X*		

[a]For subjects who prematurely terminate for any reason.
[b]Only for subjects who prematurely terminate due to an adverse even.
[c]Interim history.
[d]Site personnel will contact all subjects who do not enter the extension study approximately 70 days following drug discontinuation to determine the occurrence of adverse events.
*Applies only to Study M02-518

7.2.9 Additional Submissions, Including Safety Update

A 120-day safety update was submitted by the sponsor as an amendment to this application on April 14, 2005. Included in this amendment was safety data from PsA patients with cumulative exposure to adalimumab through November 17, 2004 from the ongoing OLE trial Study M02-537. An updated summary of the duration of adalimumab exposure for all PsA studies in the safety database is shown in Table 41. Based on the new data from the ongoing OLE study, the mean duration of adalimumab exposure in the evaluable patient population is now approximately 339 days.

Table 41 – Duration of Adalimumab Exposure for All Psoriatic Arthritis Studies

	Duration of Treatment[1] N (%)
Any Exposure	**395 (100%)**
>4 Weeks	**393 (99.5%)**
>12 Weeks	**382 (97%)**
>24 Weeks	**367 (93%)**
>36 Weeks	**348 (88%)**
>48 Weeks	**243 (62%)**
>60 Weeks	**137 (35%)**
>72 Weeks	**45 (11%)**
>84 Weeks	**1 (0.3%)**
Mean Duration of Treatment in Days[2]: 339 Days	

[1]Duration of treatment = last dose date –first dose date +1

Study M02-537's protocol permitted a dose escalation of adalimumab to 40 mg SC weekly in patients who failed to demonstrate a response to therapy at the Week 12 visit. This option was exercised in 53 patients (14%) in the study. The median duration of exposure at the higher dose for this subset was 197 days at the time this amendment was filed. A separate analysis of AEs observed in this small subset was included for review in the safety update. The following summarizes the new data contained in this 120-day safety update amendment for the total 395 PsA patients exposed to adalimumab:

- There was a slight increase in the observed incidence of treatment-emergent AEs from 74% to 84% with increased exposure to adalimumab, but the profile of events was essentially unchanged.
- The observed incidence of treatment-emergent serious AEs increased from 4% to 8% with prolonged exposure to adalimumab consistent with the longer duration of observation. There were 16 new treatment-emergent serious AEs reported as follows: appendicitis (2 cases), UTI (2 cases), diverticulitis, neuroendocrine carcinoma of the skin, cartilage injury, lymphoma, abdominal pain, salmonella gastroenteritis, infectious pericarditis, ectopic pregnancy, ovarian cyst, traumatic fracture, hip fracture, and pancreatitis. Four (2 cases of UTI, 1 case of infectious pericarditis, and 1 case of lymphoma) of these SAE cases were assessed by the investigators to be possibly-related to treatment with adalimumab.
- The observed incidence of treatment-emergent infectious AEs in the total PsA population was 50% (197/395) compared to 41% with the original submission consistent with longer exposure to the product. The pattern of infections was similar to that seen in adalimumab trials in RA patients.
- The observed incidence of treatment-emergent infectious AEs of a serious nature was 2%. There were 4 new cases of treatment-emergent serious infectious AEs reported in patients in the OLE study as follows:

  - Two cases of urinary tract infection in Subjects 518-2165 and 570-1952
  - One case of gastroenteritis secondary to salmonella infection in Subject 518-3962
  - One case of acute infectious pericarditis in Subject 518-6022
- Two new treatment-emergent malignancies (lymphoma and neuroendocrine carcinoma) were observed to have occurred in patients in the ongoing Study M02-537:
  - Subject 518-2706 is a 58 year-old female patient diagnosed with small cell lymphoma on Day 444 of treatment
  - Subject 518-0701 is a 58 year-old male patient diagnosed with neuroendocrine carcinoma on Day 256 of treatment
- One case of treatment-emergent immunologic reaction was observed in a 25 year-old female patient who developed a positive ANA (1:640) and a positive anti-dsDNA antibody (39.8; reference range 0-4.2) on Day 435 of treatment associated with a facial rash that her dermatologist attributed later to psoriasis. Study therapy was discontinued and the patient reverted to negative ANA status without sequalae.
- No cases of tuberculosis/granulomatous infections, demyelination, drug-induced lupus, or congestive heart failure were reported to have occurred
- No deaths occurred in the patients continuing to participate in the OLE trial, Study M02-537
- Overall, the percentage of patients who dropped out due to a treatment-emergent AE was 6%. The profile of events that resulted in the 11 additional patients who dropped out of the OLE study was similar to what has been seen previously in the RA databases for the product with the following exceptions:
  - A case of granuloma of the skin in a 53 year-old male (Subject 518-1461) that occurred on Day 448 of treatment following dose escalation to 40 mg weekly of adalimumab on Day 302.
  - A case of acute hepatitis in a 23 year-old male (Subject 518-2822) that occurred on Day 169 of treatment. The patient had a history of MTX-induced transaminitis which resulted in the discontinuation of the latter drug prior to entering the study. This patient was taking concomitant hepatotoxic medications (NSAIDs) and had a history of occasional alcohol ingestion. Hepatitis B and C serologies were negative. Liver sonogram revealed a cystic lesion in the right lobe; liver biopsy was consistent with mild acute hepatitis.
- The safety profile generated by the small subset of PsA patients treated with adalimumab 40 mg SC weekly was similar to that of patients treated with 40 mg SC eow.

Overall, no new safety signals were identified during the examination of the 120-day safety update. Since causality cannot be established in the one case of acute mild hepatitis (Subject 518-2822) due to the concomitant use of hepatotoxins (i.e., NSAIDs and occasional alcohol ingestion), no recommendation for adding this AE to the product's label is warranted at this time.

8 Additional Clinical Issues

8.3 Special Populations

Protocols for both Studies M02-518 and 570 prohibited pregnant women from participating in these trials. Although the studies' entry criteria required women of reproductive potential to practice effective forms of contraception for the duration of their participation in the trials, one patient (Subject 570-0152) in the ongoing OLE study had an ectopic pregnancy while participating in the study. Currently, adalimumab is classified as a pregnancy category B product. A pregnancy registry has been established for PsA patients who become pregnant while being treated with this product in order to capture these data.

8.4 Pediatrics

Since PsA is uncommon in the pediatric population, a waiver was granted by the agency in response to the sponsor's request not to study adalimumab in children.

9 Overall Assessment

9.1 Conclusions

Examination of the data submitted in support of this application has demonstrated that the benefits outweigh the potential risks for adalimumab in the treatment of the signs and symptoms of active arthritis in adults with PsA when used alone or with concomitant DMARDs. Both multicenter, double-blind, randomized, placebo-controlled studies successfully demonstrated a statistically significant difference between the two treatment groups for the primary endpoint (ACR 20 at Week 12) and in the co-primary endpoint of the pivotal study, the mTSS. These findings were supported by the results generated from a large number of secondary and ancillary parameters which assessed other areas affected by PsA besides arthritis manifestations and structural damage such as skin lesions, physical function and health related quality of life.

Adalimumab's safety profile in this patient population is similar to what has been observed previously in RA patients. No new potential safety signals were identified during the review of the safety database generated from the controlled studies and from the ongoing OLE. The positive risk/benefit ratio is supportive of approving adalimumab for the indication of PsA with the appropriate labeling.

9.3 Recommendation on Regulatory Action

This medical officer recommends approving this efficacy supplement with revisions to the proposed product label.

9.3.3 Other Phase 4 Requests

No Phase IV requests are warranted.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/45

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	BB 125057/45
Drug Name:	Humira (Adalimumab)
Indication(s):	Psoriatic Arthritis
Applicant:	Abbott
Date(s):	Date submitted: December 16, 2004
	PDUFA due date: October 16, 2005
	Review completion date: August 23, 2005
Review Priority:	Standard
Biometrics Division:	CDER/OB/BTSS
Statistical Reviewer:	Yuan Who Chen, Ph.D.
Concurring Reviewers:	Boguang Zhen, Ph.D., Statistical Team Leader
	Aloka Chakravarty, Ph.D., BTSS Staff Director
Medical Division:	HFD-108 (Internal Medicine)
Clinical Team:	Rosemarie Neuner, M.D., Medical Reviewer
	Jeffrey Siegel, M.D., Medical Team Leader
Project Manager:	Victoria TysonMedlock

Keywords: psoriatic arthritis, psoriasis, arthritis, adalimumab

Table of Contents

1. EXECUTIVE SUMMARY

BLA 125057/45 is the supplement for the indication in reducing signs and symptoms of active arthritis using adalimumab in the treatment of patients with psoriatic arthritis. The results that obtained from two Phase III pivotal studies were included in the submission as documents for Agency review.

1.1 Conclusions and Recommendations

Based upon the efficacy results that presented by the sponsor and this reviewer's statistical evaluation, BLA Supplement 125057/45 has demonstrated significant drug effect of using adalimumab in the treatment of patients with psoriatic arthritis during 12 week/24 week double-blind periods with different ACR criteria (see Table 4 on page 13). The efficacy results support the new indication claim.

1.2 Brief Overview of Clinical Studies

Adalimumab has been approved for the indication of the reduction of signs and symptoms and inhibiting the progression of structural damage in patients with rheumatoid arthritis (RA) in December 2002. An indication for improving physical function in patient with RA was approved to adalimumab in October 2003. This supplement was submitted for the indication of psoriatic arthritis (PsA). Results from two Phase III clinical trials, Study M02-518 and Study M02-570, were used to support the proposed additional indication in using adalimumab for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. An open-label, Study M02-537, was a continuation trial to enroll subjects who completed Study M02-518 or Study M02-570. More detailed information regarding study design of the two Phase III pivotal studies can be seen in later sections of this report.

1.3 Statistical Issues and Findings

- The primary efficacy variable, an ACR20 response, was defined as $\geq$ 20% improvement in swollen joint count, $\geq$ 20% improvement in tender joint, and $\geq$ 20% improvement in 3 of the 5 assessments at Week 12 from the baseline. It had been confirmed by this reviewer that the primary efficacy variable in all relevant data files was correctly derived as defined above.

- In Study M02-518, fourteen (4.5%) subjects did not complete Week 12 visit. In the primary analysis of ACR20 response, those missings at Week 12 were treated as non-responders. In addition, the missing ACR20 components were treated as non-response. Table 6 (see page 17) presents the missing counts by ACR20 component at baseline, Week 12 and Week 24. No unusual difference of missing counts between two treatment groups observed. Several sensitivity analyses were conducted that confirmed the robustness of the primary efficacy results.

- Primary efficacy should be sustained from Week 12 to Week 24 clinically. Data from Study M02-518 showed that 88.5% (77 of 87) of those who were responders at Week 12 of the adalimumab-treated subjects still kept the responder status at Week 24. In contrast, only 43.5% (10 of 23) of placebo subjects were responders at Week 12 and also at Week 24. It appears that the primary efficacy for the adalimumab subjects sustained at Week 24, the end of double-blind period, in Study M02-518. There was no 24 week double-blind data collected in Study M02-570.

- The subgroup analysis by country was not documented in the sBLA submission. Both of the two pivotal studies were international trials. In Study M02-518 and Study M02-570, 155 (49.5%) and 66 subjects (66.7%) were recruited from the US sites, respectively, and 76 (24.3%) and 33 subjects (33.3%) were recruited from Canadian sites. Subgroup analysis by country was performed by this reviewer. The analysis results showed that the primary efficacy was retained among those US subjects and among those subjects from Canada or other countries consistently (see Table 5 on page 17).

- It was documented in the submission that in Study M02-518 the blinded joint assessor at one site was discovered to also be performing other assessments (N=13). Two investigators had received significant payments from the sponsor other than payments for conducting the clinical studies (N=7 & N=12, respectively). And 7 subjects (6 placebo subjects and 1 adalimumab subject) received rescue therapy although they did not qualify per protocol criteria.

  An efficacy analysis has been conducted with excluding the 38 subjects mentioned above (Note: One subject received rescue whom was recruited by one of the two investigators). The efficacy result from the rest subjects (N=275) was very similar as that from the primary efficacy analysis. The ACR20 response rates were 15% and 57% ($p < 0.001$) for placebo and adalimumab groups, respectively.

- There were two co-primary efficacy endpoints in Study M02-518. Multiplicity was not an issue in this study since both two co-primary endpoints were highly significant with p-values < 0.001. In addition, the results from radiograph data will not be used for labeling change in this submission.

2. INTRODUCTION

2.1 Overview

Psoriatic arthritis (PsA) is an inflammatory arthropathy associated with psoriasis. The course of PsA is usually characterized by flares and remissions. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy. For most patients, skin manifestations preceed the arthritis.

Psoriatic arthritis patients require treatments for both skin and joint manifestations of this disease. More severe disease can be treated with disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX). The goal of PsA treatment is to decrease signs and symptoms of PsA, inhibit the structural damage to joints, improve the skin lesions of psoriasis, and improve the quality of life.

Adalimumab, a recombinant, human immunoglobulin G1 (IgG1) monoclonal antibody, contains exclusively human sequences and is specific for TNF-α. Adalimumab has been approved for the treatment of rheumatoid arthritis (RA) in adult patients in the US, European Union, and in 25 additional countries as of 30 June 2004. This supplement was submitted for the indication of psoriatic arthritis which included two Phase III studies, M02-570 and M02-518.

Study M02-518 was a Phase III, placebo-controlled, double-blind, randomized, multicenter study to evaluate the safety and efficacy of adalimumab in the treatment of moderate to severely acute PsA in subjects who had ≥ 3 swollen joints and ≥ 3 tender joints and had an inadequate response to NSAID therapy. Subjects on active treatment received a subcutaneous injection of 40 mg adalimumab every other week with a 24-week treatment period. A total of 315 subjects were enrolled at 50 sites in the US (N=155), Canada (N=76), Germany (N=9), Italy (N=2), UK (N=19), France (N=11), Austria (N=4), and Belgium (N=38). Among those, 313 subjects received at least one inject of study drug, and 289 subjects completed the study. Subjects were stratified for methotrexate (MTX) use and extent psoriasis, and randomized in a 1:1 ratio by site to receive either adalimumab or placebo. Duration of the treatment period in the study was 24 weeks.

The primary efficacy endpoint was ACR20 response at Week 12. A co-primary efficacy endpoint was joint destruction at Week 24, which was evaluated using the mean change in the modified total Sharp scores (mTSS). This co-primary endpoint will not be used for any labeling claim (b) (4) The one year duration data will be submitted to the Agency later as another supplemental BLA.

Study M02-570 was a Phase III, placebo-controlled, double-blind, randomized, multicenter, multination study to evaluate the safety and efficacy of adalimumab in the treatment of moderate to severely acute PsA in subjects who had ≥ 3 swollen joints and ≥ 3 tender joints and had an inadequate response to disease-modifying anti-rheumatic drug (DMARD) therapy. Similar to Study M02-518, subjects on active treatment in this study received a subcutaneous injection of 40 mg adalimumab every other week. The treatment period was 12 weeks.

A total of 102 subjects were recruited from 16 sites in the US (N=67) and Canada (N=33), and 96 subjects completed the study. Subjects were stratified for DMARD use at baseline, and randomized in a 1:1 ratio to receive either adalimumab or placebo. The primary efficacy endpoint was ACR20 response at Week 12.

Study M02-537 is an open label, multicenter continuation trial for subjects completing Study M02-518 or Study M02-570 to evaluate the long-term safety and efficacy of re-treatment of adalimumab. The study was still on-going at the time of this sBLA was submitted to the Agency. Only an interim report of the study was included in the submission.

Study M02-518 and Study M02-570 were the two Phase III trials designed to evaluate safety and efficacy of adalimumab for the new indication of PsA. Both of the two studies are selected for statistical review.

2.2 Data Sources

Data were provided by the sponsor electronically. All of the data are located in CDER Electronic Document Room (http://10.3.16.9/rs-bin/RightSite.dll/ssi4_logged_in) with STN #125057/45. The efficacy and safety data files and SAS program codes can be found in bla125057\CRT folder. The CRT folder contains two sub-folders, "Analysis Ready" folder which includes files and variables for final efficacy and safety analyses and the "Datasets" folder which includes all non-derivative variables.

3. STATISTICAL EVALUATION

This report includes the detailed review of two pivotal trials, Study M02-518 and Study M02-570.

3.1 Evaluation of Efficacy

Two Phase III pivotal studies were included in the sBLA submission. There were minor differences between the two Phase III studies in study design. In this report, design of study, statistical method, sample size estimation and efficacy endpoints are addressed separately for each study. However, the baseline characteristics, ACR components at baseline, and efficacy results for the two studies are listed and contrasted in same tables. The modified total Sharp Score (mTSS) and its components were not collected in Study M02-570. Table 3 shows the mTSS scores and components for Study M0-518 only.

3.1.1 Study Design and Endpoints for Study M02-518

Study M02-518 was a Phase III, placebo-controlled, double-blind, randomized, multicenter study to evaluate the safety and efficacy of adalimumab in the treatment of moderate to severely act PsA in subjects who had ≥ 3 swollen joints and ≥ 3 tender joints and had an inadequate response to NSAID therapy. Subjects on active treatment received a subcutaneous injection of 40 mg adalimumab or matched placebo every other week with a 24-week treatment period.

The duration of the study was up to 26 weeks, including up to a 2-week screening period and a 24-week treatment period. Subjects discontinuing the study due to an adverse

event were asked to return to the study site 30 days post-final dose for a follow-up visit. All subjects completing the study were eligible for open-label therapy in Study M02-537 following the Week 24 visit. Subjects who failed to respond were allowed to receive rescue treatment with corticosteroids or DMARDs. The earliest time for subject allowed to receive rescue therapy was at the Week 12 visit.

The primary analysis was to focus on the intent-to-treat (ITT) patient population, defined as all subjects who received at least one dose of study treatment. All statistical tests were to be two-sided at $\alpha = 0.05$.

Determination of Sample Size: The sample size calculation was based on the hypothesis test for the primary efficacy endpoint of change in modified total Sharp score, which yielded the more conservative estimate of sample size. A sample size of 150 subjects per treatment group with non-missing data resulted in 80% statistical power to detect an effect size (mean difference between treatment groups divided by the pooled standard deviation) of 0.325.

Randomization Study: Subjects were stratified by MTX use (yes, no) and degree of psoriasis involvement (≥3% BSA or <3% BSA) at baseline, and then randomized in a 1:1 ratio by site to receive either adalimumab or placebo.

A total of 315 subjects were enrolled at 50 sites in the US, Canada, Germany, Italy, UK, France, Austria, and Belgium. Among those, 313 subjects received at least one inject of study drug, and 289 subjects completed the study.

Primary Efficacy Endpoints: The primary efficacy endpoint was ACR20 response at Week 12. A co-primary efficacy endpoint was joint destruction at Week 24, which was evaluated using the mean change in the modified total Sharp scores.

Secondary Efficacy Endpoints: ACR20 response rate at Week 24, ACR50/70 response rates at Weeks 12 and 24, Modified PsARC at Weeks 12 and 24, Disability Index of HAQ at Weeks 12 and 24, SF-36 Health Status Survey at Weeks 12 and 24, Change in Sharp score components at Week 24, Proportion of subjects with no change in modified total Sharp score at Week 24, and Changes in radiographic findings specific to psoriatic arthritis at Week 24.

3.1.2 Study Design for Study M02-570

Study M02-570 was a Phase III, placebo-controlled, double-blind, randomized, multicenter study. Subjects received a subcutaneous injection of 40 mg adalimumab every other week within a 12-week unblinded treatment period. No X-ray data were collected in this study. All subjects completing the study were eligible for an open label therapy in Study M02-537 following the Week 12 visit.

Determination of Sample Size: The sample size calculation was based on the assumptions of an ACR20 response rate of 60% in the 40 mg group, 25% in the placebo

group. The level of significance was set as $\alpha = 0.05$. A total of 100 subjects (50 subjects per treatment group) provide > 90% power.

Randomization: Subjects were stratified by DMARD use at baseline, and then randomized by site in a 1:1 ratio to receive either 40 mg adalimumab every other week or placebo. Subjects were randomized in blocks of 4 subjects per block. A total of 102 subjects were recruited from 16 sites in the US and Canada, and 96 subjects completed the study.

Primary and secondary efficacy endpoints: The primary efficacy endpoint was ACR20 response at Week 12, which is the same as one of the two co-primary efficacy endpoints of Study M02-518. The secondary efficacy endpoints included: ACR50/70, Modified Psoriatic Arthritis Response Criteria (PsARC), Disability Index of the Health Assessment Questionnaire (HAQ), SF-36, and Functional assessment of chronic illness therapy (FACIT) fatigue.

The primary analysis was to focus on the intent-to-treat (ITT) patient population, defined as all subjects who received at least one dose of study treatment. All statistical tests were two-sided at $\alpha = 0.05$.

3.1.3 Patient Disposition, Demographic and Baseline Characteristics (Studies M02-518 and M02-570)

Patient disposition and baseline patient characteristics are discussed here for the two pivotal studies and presented in Tables 1-3. Table 3 includes the modified total Sharp score and the components at baseline for Study M02-518 only since the mTSS data was not collected in Study M02-570.

A total of 313 and 102 subjects were randomized into either placebo or adalimumab group and 299 and 96 subjects completed Week 12 visit in Study M02-518 and Study M02-570, respectively. Among those 299 subjects who completed Week 12 visit in Study M02-518, 289 subjects completed Week 24 visit.

In details, 13 (8.0%) placebo subjects and 11 (7.3%) adalimumab group subjects dropped out from study prior to Week 24 visit in Study M02-518, and 3 (6.1%) placebo subjects and 1 (2.0%) adalimumab subject did not finish Week 12 visit. Two subjects in adalimumab group of Study M02-518 and two placebo subjects in Study M02-570 were randomized but did not receive any drug treatment.

The majority of subjects, 95.5% in Study M02-518 and 96.0% in Study M02-570, were Caucasian. The gender distributions were similar between placebo and adalimumab group for both two pivotal studies. Table 1 presents percentages of patient population by demographic and baseline characteristics for the two studies.

It appears that patient populations in both studies were well-matched between adalimumab and placebo groups for the baseline factors listed in Tables 1-3.

Table 1. Demographic and Baseline Characteristics (Study M02-518 & Study M02-570)

	Study M02-518			Study M02-570		
	Placebo (N=162)	Adalimumab (N=151)	p-value	Placebo (N=49)	Adalimumab (N=51)	p-value
Gender						
Female	75 (45.1%)	66 (43.7%)	0.821	24 (49.0%)	22 (43.1%)	0.688
Male	89 (54.9%)	85 (56.3%)		25 (51.0%)	29 (56.9%)	
Race						
Caucasian	152 (93.8%)	147 (97,4%)	0.174	46 (93.9%)	50 (98.0%)	0.357
Non-Caucasian	10 (6.2%)	4 (2.6%)		3 (6.1%)	1 (2.0%)	
Country						
US	83 (51.2%)	72 (47.7%)	0.821	32 (65.3%)	34 (68.0%)	0.776
Canada	38 (23.5%)	38 (25.2%)		17 (34.7%)	16 (32.0%)	
Others	41 (25.3%)	41 (27.1%)				
Age						
< 40	31 (19.1%)	36 (23.8%)	0.080	14 (28.6%)	9 (17.6%)	0.153
40-64	119 (73.5%)	104(68.9%)		32 (65.3%)	38 (74.5%)	
65-74	11 (6.8%)	5 (3.3%)		1 (2.0%)	4 (7.8%)	
≥ 75	1(0.6%)	6 (4.0%)		2 (4.1%)	0 (0%)	
Age						
Mean ± SD	49.2±11.1	48.6±12.5	0.652	47.7±11.3	50.4±11.0	0.236
Median (Range)	51 (21-79)	49 (20-88)		46 (29-79)	50 (25-73)	
Body Weight (kg)						
Mean ± SD	85.5±16.5	86.0±20.6	0.806	88.5±21.1	91.5±22.5	0.506
Median (Range)	85.3 (45-135)	85.0 (47-156)		87.1 (49-154)	89.0 (50-151)	
Baseline MTX Use	81 (50.0%)	77 (51.0%)	0.910	N/A	N/A	
Baseline DMARD Use	N/A	N/A		33 (67.3%)	35 (68.6%)	0.999
Duration of PsA (yrs)						
Mean ± SD	9.2±8.8	9.8±8.3	0.518	7.2±7.0	7.5±7.0	0.838
Median (Range)	6.9 (0-52.8)	8.0 (0-40.1)		5.3 (0.1-27.5)	6.0 (0.1-25.3)	
Druation of Psoriasis (yrs)						
Mean ± SD	17.4±12.6	17.2±12.0	0.936	13.8±10.7	18.0±13.2	0.085
Median (Range)	14.0 (0.2-57.8)	14.3 (0.6-56.1)		9.3 (0.1-51.3)	15.3 (0-57.3)	
Spondylitis						
Yes	24 (14.8%)	39 (19.2%)	0.366	10 (20.4%)	10 (19.6%)	0.999
No	138 (85.2%)	122 (80.8%)		39 (79.6%)	41 (80.4%)	

Since ACRn is a composite criterion which is defined as: ≥ n% improvement in swollen joint count, ≥ n% improvement in tender joint count, and ≥ n% improvement in 3 of the 5 assessments (patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, CRP, and disability Index of HAQ), the baseline data of swollen joint count, tender joint count and the 5 assessments are important for the result of ACRn response and should be balanced between adalimumab-treated group and placebo at the baseline. Table 2 shows the baseline ACR components data. Only adalimumab group had a lower baseline CRP than placebo in Study M02-570.

In Table 3, baseline modified total Sharp score and the two components (Study M02-518) are presented. None of them were statistically significantly different between the two groups.

Table 2. ACR Components at Baseline

	Study M02-518			Study M02-570		
	Placebo (N=162)	Adalimumab (N=151)	p-value	Placebo (N=49)	Adalimumab (N=51)	p-value
Tender Joint Count						
Mean ± SD	25.8±18.0	23.9±17.3	0.336	29.3±18.1	25.3±18.3	0.281
Median (Range)	23 (3-75)	20 (2-74)		25 (5-70)	19 (3-78)	
Swollen Joint Count						
Mean ± SD	25.8±18.0	23.9±17.3	0.336	18.4±12.1	18.2±10.9	0.936
Median (Range)	11 (0-64)	11 (0-60)		15 (3-60)	17 (3-43)	
Patient's Assessment of Pain (VAS)						
Mean ± SD	48.8±21.7	51.1±21.4	0.345	49.1±23.5	43.3±23.4	0.224
Median (Range)	49 (0-98)	54 (1-96)		51 (9-98)	42 (7-97)	
Patient's Global Assessment of Disease Activity (VAS)						
Mean ± SD	48.1±21.2	47.1±23.2	0.688	46.3±24.6	42.9±22.4	0.473
Median (Range)	49 (0-96)	48 (2-95)		48 (4-96)	45 (2-98)	
Physician's Global Assessment of Disease Activity (VAS)						
Mean ± SD	53.5±15.7	53.8±15.7	0.946	57.1±16.2	52.5±17.1	0.177
Median (Range)	53 (12-97)	55 (11-89)		56 (29-88)	53 (17-86)	
CRP						
Mean ± SD	1.4±1.7	1.4±2.1	0.832	1.6±1.7	1.0±1.0	0.021*
Median (Range)	0.8 (0-10)	0.8 (0-16)		0.9 (0-7)	0.7 (0-5)	
Disability Index of HAQ						
Mean ± SD	1.0±0.7	1.0±1.0	0.544	1.0±0.7	0.9±0.5	0.347
Median (Range)	1.0 (0-2.6)	1.0 (0-2.5)		0.9 (0-2.5)	1.0 (0-2.4)	

Table 3. Modified Total Sharp Score and Components at Baseline (Study M02-518)

	Study M02-518		
	Placebo (N=162)	Adalimumab (N=151)	p-value
Modified Total Sharp Score			
Mean ± SD	19.1 ± 35.5	22.7 ± 46.0	0.445
Median (Range)	5.5 (0-223)	7.6 (0-348)	
Joint Space Narrowing Score			
Mean ± SD	9.2 ± 16.9	11.2 ± 21.9	0.351
Median (Range)	2.5 (0-109)	3.6 (0-157)	
Erosion Score			
Mean ± SD	10.0 ± 19.7	11.4 ± 25.5	0.566
Median (Range)	2.0 (0-114)	2.8 (0-191)	

3.1.4 Statistical Methodologies

Primary Efficacy Analyses (Study M02-518): The response rate of ACR20 at Week 12 and the change from baseline of the modified total Sharp score for radiographic progression at Week 24 were the primary efficacy variables. In the protocol, the sponsor proposed to test the two primary efficacy variables in a hierarchical order, i.e. the ACR20 at Week 12 was tested for statistical significance first and testing for statistical significance in radiographic progression would be carried out only if the result of ACR20 at Week 12 was statistically significant.

The analysis for the first primary endpoint was a comparison between treatment groups of the proportion of ACR20 responders at Week 12 using the Cochran Mantel Haenszel test adjusted for MTX use and extent of psoriasis. Those with missing data were to be included in the analysis as non-responders. A supportive analysis of the ACR20 results was to be provided using the Last Observation Carried Forward (LOCF) approach to impute missing values.

A comparison between treatment groups of the mean change from baseline of the modified total Sharp score at Week 24 was used to analyze the secondary co-primary efficacy endpoint. The treatment difference was evaluated using an analysis of covariance (ANCOVA) method with baseline Sharp score, MTX use and extent of psoriasis as covariates.

Secondary Efficacy Analyses (Study M02-518): The ACR20 at Week 24 and ACR50/70 at Weeks 12 and 24 were described using counts and percentages; Cochran Mantel Haenszel test adjusted for MTX use and extent of psoriasis test was used to assess treatment group differences. Identical methods were used to evaluate modified PsARC, proportion of subjects with no change in modified total Sharp score, and PASI 50/75 in subjects with ≥ 3% BSA psoriasis involvement results. The change from baseline in

HAQ, SF-36 and mTSS components in all subjects, and change from baseline in DLQI and Physician's Global Assessment for Psoriasis in subjects with 3% BSA psoriasis involvement were assessed between treatment groups using analysis of variance (ANOVA). The ANOVA model included factors for MTX use, the extent of psoriasis and treatment.

Review Comment: The Agency concluded that the 24-week time length was not sufficient to observe the treatment effect in the progression of PsA. All 24-week radiograph data were not used for any labeling claim in this submission.

Efficacy Analysis for Study M0-570: The ACR20 response at Week 12 was the primary efficacy endpoint of the study. The Cochran-Mentel-Haenszel test adjusted for MDARD use as the covariate was used for the primary efficacy analysis..

Similar statistical methods as those described in Study M02-518 were used to evaluate the effect of 40 mg every other week adalimumab compared to placebo at Week 12 on: ACR50/70, Modified Psoriatic Arthritis Response Criteria (PsARC), Disability Index of the Health Assessment Questionnaire (HAQ), SF-36, and Functional Assessment of Chronic Illness Therapy (FACIT) fatigue.

3.1.5 Results and Conclusions

The ACR20 response at Week 12 in both two pivotal studies was statistically significant in favor to adalimumab treatment, with $p<0.001$ and $p=0.012$ for Study M02-518 and Study M02-570, respectively. The co-primary efficacy endpoint of the modified total Sharp score at Week 24 in Study M02-518 was statistically significant with $p<0.001$.

The secondary efficacy endpoints, ACR50/70 responses at Week 12, were all statistically significant in both two studies. Table 4 presents ACR20/50/70 responses at Week 12 for both studies and ACR20/50/70 responses at Week 24 for Study M0-518 only.

In addition, Figure 1 on page 15 of this report shows ACR20, ACR50 and ACR70 responses by visit, from baseline to Week 24 for Study M02-518. The ACR20/50/70 responses from baseline to Week 12 for Study M02-570 were somewhat similar but less significant in group difference. Figure 1 was duplicated from the sponsor's submission.

Table 4. ACR20, ACR50, and ACR 70 Responses at Week 12 and Week 24 by Treatment Group (Study M02-518 and Study M02-570)

	Study M02-518			Study M02-570		
	Placebo (N=162)	Adalimumab (N=151)	p-value	Placebo (N=49)	Adalimumab (N=51)	p-value
ACR20 at Week 12						
Proportion	0.14	0.58	<0.001	0.16	0.39	0.012
Difference	0.44			0.23		
95% CI	(0.33, 0.54)			(0.05, 0.41)		
ACR20 at Week 24						
Proportion	0.15	0.57	<0.001			
Difference	0.42			N/A		
95% CI	(0.31, 0.52)					
ACR50 at Week 12						
Proportion	0.04	0.36	<0.001	0.02	0.25	<0.001
Difference	0.33			0.23		
95% CI	(0.24, 0.42)			(0.05, 0.37)		
ACR50 at Week 24						
Proportion	0.06	0.39	<0.001			
Difference	0.42			N/A		
95% CI	(0.24, 0.43)					
ACR70 at Week 12						
Proportion	0.01	0.20	<0.001	0.00	0.14	0.013
Difference	0.19					
95% CI	(0.13, 0.26)					
ACR70 at Week 24						
Proportion	0.01	0.23	<0.001			
Difference	0.21			N/A		
95% CI	(0.14, 0.28)					

Sensitivity Analysis for Study M02-518: Fourteen (4.5%) and 3 (3.0%) subjects did not completed Week 12 in Study M02-518 and Study M02-570, respectively. In the primary analysis of ACR20 response, those missings at Week 12 were treated as non-responders. The sponsor conducted two different analyses to assess the robustness of the primary efficacy result by using worst-case method and modified worst-case method (considered placebo dropouts as responders only if exhibited a response at any time prior to dropout and all adalimumab dropouts were considered as non-responders). The results from those sensitivity analyses were also confirmed the treatment effect of adalimumab ($p<0.001$)

Twenty (6.4%) subjects withdrew from Study M02-518 before the end of Week 24. Results from several sensitivity analyses of the secondary co-primary efficacy endpoint were reported in the submission. Those methods of sensitivity analysis included: imputing the 50th percentiles, using logarithm/square root of actual total sharp score, using re-reads, imputing a zero change from baseline, imputing the worst rank, completed cases analysis, and evaluable cases analysis. Those sensitivity analyses provided with

similar results to demonstrate the robustness of the primary efficacy of modified total Sharp scores at Week 24.

Sensitivity Analysis for Study M02-570: Several sensitivity analyses of the ACR20 response at Week 12 were performed. Results of the worst case and the modified worst case sensitivity analyses of the ACR20 response at Week 12 were consistent with the primary efficacy analysis of Week 12 ACR20 response ($p=0.012$). For subjects completing the study (46 of the placebo subjects and 50 of the adalimumab subjects), the adalimumab group was statistically superior to the placebo group ($p = 0.017$).

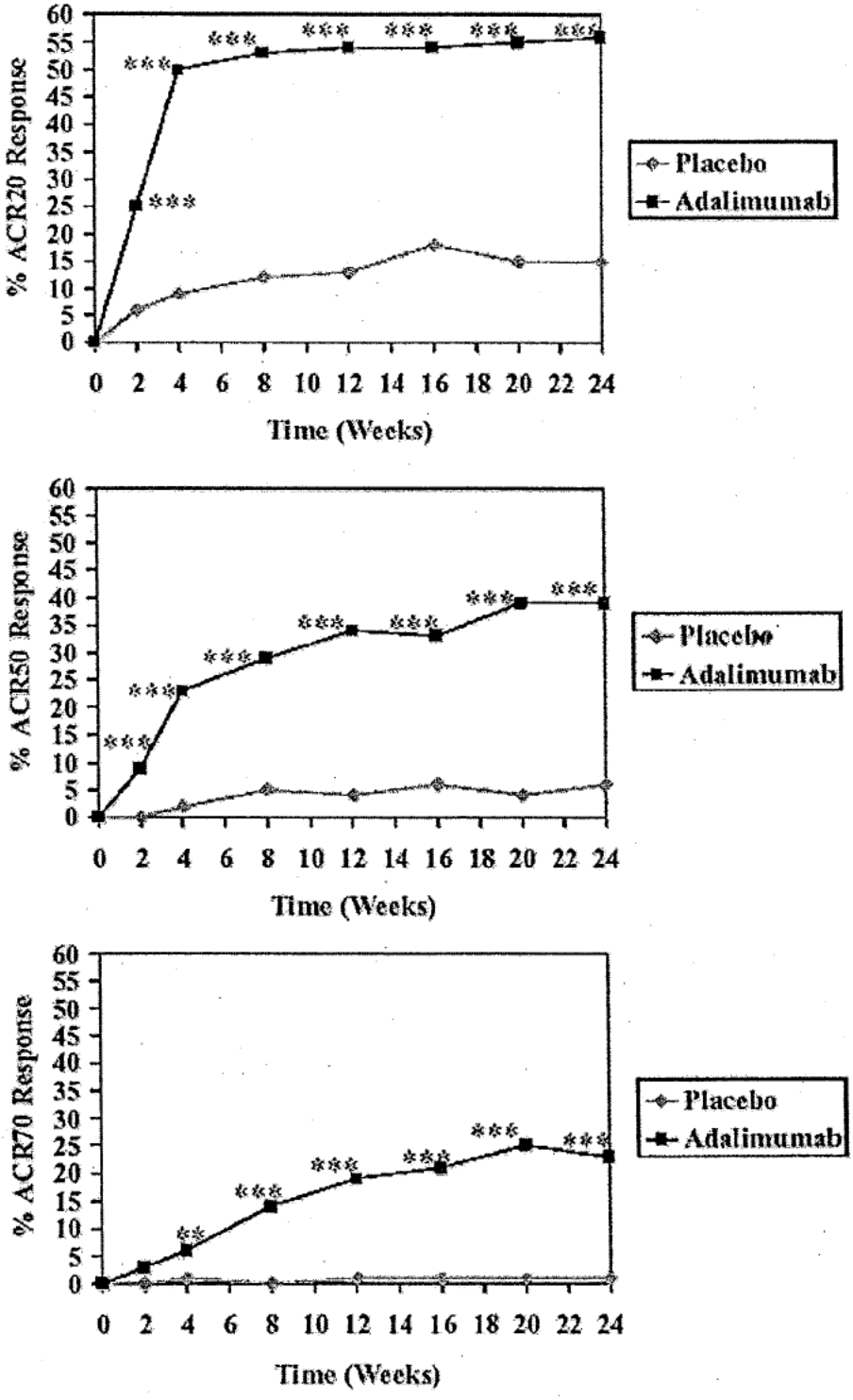
Secondary Efficacy Results: In additional to ACR20/50/70, the data of Study M02-518 showed that the PsARC at Week 12 and Week 24 adjusted for MTX use at baseline and % BSA, disability index of HAQ at Week 12 and Week 24, and PASI 50/75 at Week 12 and Week 24 were all significant with p-values < 0.001 in favor to the treatment effect of adalimumab group.

The data of Study M02-570 showed consistent results from secondary efficacy analyses as the primary efficacy analysis. The ACR50 response at Week 12 was 25% for adalimumab vs 2% for placebo ($p<0.001$) and the ACR 70 response at Week 12 was 14% for adalimumab vs 0% for placebo ($p=0.013$). The PsARC response at Week 12 was 51% for adalimumab vs 24% for placebo ($p=0.007$). In addition, the disability index of HAQ ($p=0.027$), PGA ($p=0.003$), and target lesion score ($p<0.001$) showed significant improvement of adalimumab treatment effect.

3.2 Evaluation of Safety

The evaluation of safety can be seen in the medical reviewer's report.

Figure 1. ACR20, ACR50, and ACR70 Responses by Visit (Study M02-518)



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Since the majority of subjects (96%) in both studies were Caucasians, the ACR20 responses by race subgroup were not presented in Table 5. The cutoff of age < 40 and ≥ 40 was used for the age subgroups presented in Table 5 was based upon the sample size consideration. Although several subgroups in Study M02-570 did not show significant adalimumab effect, such as female, age < 40, Canadians, and without using DMARD at baseline, the observed % ACR20 responses of adalimumab group were higher than those of placebo, respectively.

Table 5. ACR20 Responses at Week 12, by Treatment Group, Overall and by Subgroup (Study M02-518 and Study M02-570)

ACR20 Response at Week 12	Study M02-518			Study M02-570		
	Placebo (N=162)	Adalimumab (N=151)	p-value	Placebo (N=49)	Adalimumab (N=51)	p-value
Overall	0.14	0.58	<0.001	0.16	0.39	0.011
Gender						
Female	0.15	0.58	<0.001	0.17	0.23	0.605
Male	0.14	0.58	<0.001	0.16	0.52	0.006
Age						
< 40	0.13	0.81	<0.001	0.14	0.33	0.280
≥ 40	0.15	0.53	<0.001	0.19	0.45	0.021
Country						
US	0.12	0.60	<0.001	0.19	0.41	0.048
Canada	0.05	0.52	<0.001	0.12	0.38	0.085
Other	0.27	0.59	0.004	N/A	N/A	
Baseline MTX/DMARD Use						
Yes	0.10	0.55	<0.001	0.18	0.40	0.048
No	0.19	0.61	<0.001	0.13	0.38	0.103

4.2 Other Special/Subgroup Populations

Table 4 also presents ACR20 response rates at Week 12 by country, by baseline MTX or DMARD use for the two pivotal studies. In both studies, the US subjects and Canadian subjects presented consistent ACR20 response rates individually. In Study M02-570, the Canadian subgroup did not show a statistically significant result because of the size of sample, but it still presented a similar magnitude of ACR20 response difference between adalimumab group and placebo as that of the US subgroup.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For the analyses for ACR20/50/70 response, subjects who early terminated and missing data with ACR components might lead to a biased between group difference. Table 6 lists the missing numbers of subjects in ACR20 components at baseline, Week 12 and Week 24 for Study M02-518. Based on the missing number of subjects in Table 5, there were no unusual observed difference between adalimumab group and placebo for all ACR components. This reviewer concluded that missing data should not lead to bias the primary efficacy result in Study M02-518.

Only 3 subjects dropped out from Study M02-570 before Week 12. Two of those were placebo subjects. It is not necessary to list all missing counts for the ACR components for Study M02-570.

Table 6. Summary of Subjects with Missing Values for ACR20 Components (Study M02-518)

	Week 0		Week 1 2		Week 24	
	Placebo	**Adalimumab**	**Placebo**	**Adalimumab**	**Placebo**	**Adalimumab**
Total N	162	151	162	151	162	151
Swollen Joint Count	0 (0.0%)	0 (0.0%)	8 (4.9%)	8 (5.3%)	15 (9.3%)	15 (9.9%)
Tender Joint Count	0 (0.0%)	0 (0.0%)	8 (4.9%)	8 (5.3%)	15 (9.3%)	15 (9.9%)
Pain VAS	1 (0.0%)	0 (0.0%)	9 (5.6%)	9 (6.0%)	16 (9.9%)	16 (10.6%)
Patient's Global VAS	1 (1.0%)	0 (0.0%)	9 (5.6%)	10 (6.6%)	16 (9.9%)	16 (10.6%)
Physician's Global VAS	1 (1.0%)	2 (1.3%)	15 (9.3%)	15 (9.9%)	18 (11.1%)	18 (11.9%)
HAQ	0 (0.0%)	0 (0.0%)	8 (4.9%)	9 (6.0%)	17 (10.5%)	17 (11.3%)
CRP	0 (0.0%)	0 (0.0%)	9 (5.6%)	13 (8.6%)	17 (10.5%)	17 (11.3%)

Other statistical issues: Both two pivotal studies did not have any issues with regards to inconsistency results across subgroups, Type I error inflation, unblinded or unplanned interim analyses, and change of primary endpoint or number of arms during conduct the trial. There were two co-primary efficacy endpoints in Study M02-518. Multiplicity was not an issue in this study since both two co-primary endpoint were highly significant with p-values < 0.001. No interim analyses were performed during either Study M02-518 or Study M02-570.

5.2 Conclusions and Recommendations

The primary endpoint, proportion of ACR20 response, demonstrated a statistically significant treatment efficacy of adalimumab when compared with placebo. ACR20/50/70 responses also presented consistent results over time in Week 12/Week 24 double-blind period. Subgroup analyses provided with consistent efficacy results of ACR20 response in age, gender, region and baseline MTX/MDARD use. The efficacy data were focused on Caucasians.

The adalimumab group also demonstrated statistical significance for the secondary efficacy endpoints at Week 12 and Week 24. Results from both Study M02-518 and Study M02-570 were consistent.

Based upon the consistent efficacy results from the primary and the secondary efficacy analyses, at different time points, and results from several subgroup analyses, this supplemental BLA application has demonstrated significant efficacy of using adalimumab in the treatment of patients with psoriatic arthritis.

Primary Statistical Reviewer: **Yuan Who Chen, Ph.D.**
Date: **August 19, 2005**

Concurring Reviewer(s):

8/24/05

Statistical Team Leader: **Boguang Zhen, Ph.D.**

9/6/05

Biometrics Division Director: **Aloka Chakravarty, Ph.D.**

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APPLICATION NUMBER:

BLA 125057/45

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

06/27/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 125057/45 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: 12-16-04 **Action Date:** 10-16-05

HFM 108 **Product and Proprietary names/dosage form:** _____

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

Indication(s) previously approved:
Waiver requested; low prevalance

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

Number of indications for this application(s): 1

Indication #1: Rheumatoid athritis

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

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

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**	

Reason(s) for partial waiver:

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

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

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

Comments: Testing, testing, testing, testing, Testing, testing, testing, testing, Testing, testing, testing, testing, Testing, testing, testing, testing, Testing, testing, testing, testing,

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

This page was completed by:

_____
Regulatory Project Manager

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

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

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

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
LETTER:

Summary Text: Clinical Supplmt. Efficacy - Expanded Indication

LETTER: Pediatric Waiver Granted (PWG)

REVIEW COMPLETION REQUIRED BY: RIS

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

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

cc: Attached label is sent to everyone
HFD-108/M. Walton
HFD-108/J. Siegel
HFD-108/R. Neuner
HFD-109/E. Laughner
HFD-109/K. Schneider
HFM-597/Y-W Chen
HFD-580/ S. Tran
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FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 34 **(Including Cover Page)**

FAX TO: James Steck, Abbott

Facsimile Telephone No. 847-887-8251 **Voice Telephone No.** 847-937-0335

FROM: Erik S. Laughner, M.S.

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

DATE: 10/03/05 **TIME:**

MESSAGE: Label

telecon

Teleconference Memorandum

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

Discussion:

Left voicemail message with Jim Steck that the Agency (b) (4)

telecon

Teleconference Memorandum

Date:	09-23-05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Rosemarie Neuner, Jeff Siegel
Re:	Adalimumab
STN:	125057.45

Discussion:

Re-run the [redacted] (b) (4)

TELECONFERENCE

Date:	September 13, 2005
Time:	1:30 P.M.
Sponsor:	Abbott
Re:	s-BLA 125057/45
Participants:	Jeffrey Siegel (FDA) Jim Steck (Abbott) (b) (6) (Abott) John Meddich (Abbott)
Discussion:	In this teleconference we had general discussions on the draft package insert.

telecon

Teleconference Memorandum

Date:	08/25/05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Rosemarie Neuner
Re:	Adalimumab
STN:	125057.45

Discussion:

A follow-up teleconference from the following day resulted in a request for statistical output tables and Word tables for LOCF analyses of ACR core component data, Week 12 and 24, for Studies M02 - 518 andM02 - 570, respectively.

telecon

Teleconference Memorandum

Date:	08/24/05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Rosemarie Neuner
Re:	Adalimumab
STN:	125057.45

Discussion:

I spoke with Jim Steck on perceived discrepancies related to differences between the median values in the draft PsA Labeling Table 5 and Tables 3and 5 of the July 8, 2005 submission (Amendment 4 to BLA 125057/45) that included LOCF median analyses for ACR Core Components.

telecon

Teleconference Memorandum

Date:	08/17/05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Rosemarie Neuner, Yuan Chen
Re:	Adalimumab
STN:	125057.45

Discussion:

1. Provide source data sets to confirm the following sentence in Section 10.2 of the M02-518 Clinical Study Report (CSR): "Of note, six placebo-treated subjects and two adalimumab-treated subjects received rescue therapy although they did not qualify per protocol criteria."

2. Provide the study site number for the Veys site also mentioned in Section 10.2 of the M02-518 CSR.

telecon

Teleconference Memorandum

Date:	06/28/05
Sponsor Participants:	Jim Steck / Abbott (847)-937-0335
FDA Participants:	Victoria Tyson-Metlock
Re:	Adalimumab
STN:	125057.45

Discussion:

Sponsor was asked to provide:

1. M02-518

- Re-run the subgroup analysis for American College of Rheumatology 20 (ACR20) Response at Week 12 (Table 36 from the M02-518 clinical study report [CSR]) for age, weight, and duration of psoriatic arthritis (PsA) using quartiles.

- Re-run the subgroup analysis for modified total Sharp score (mTSS) at Week 24 (Table 37 from the M02-518 CSR) for age and weight using quartiles. An analysis for duration of PsA using quartiles is also supplied.

- Re-run the ACR Core Set at Week 12 and Week 24 (Table 34 from the M02 - 518 CSR) using the last observation carried forward (LOCF) analysis showing Baseline and median percent (%) change.

2. M02-570

- Re-run the subgroup analysis for ACR20 Response at Week 12 (from the M02-570 CSR) for age, weight, and duration of PsA using quartiles.

- Re-run the ACR Core Set at Week 12 (from the M02-570 CSR) using the LOCF analysis showing Baseline and median % change.

3. Safety

For subjects with Common Toxicity Criteria (CTC) Grade 3 and 4 liver function test (LFT) abnormalities, provide:

- Case numbers and narratives that include any risk factors for LFT abnormalities including things such as alcohol abuse, hepatitis, other hepatotoxic drugs *(e.g.,* methotrexate, sulfonamides, etc. . .)

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

Memorandum

Teleconference Date: June 22, 2005 **Time: 3:00 p.m.**

Sponsor: Abbott Laboratories

Product: Adalimumab [Humira]

STN 125057/45- to expand the indication to include psoriatic arthritis

Proposed Use: Psoriatic arthritis

Teleconference Purpose: Information request

Dr. Rosemarie Neuner and I called Abbott Laboratories and asked that they submit clinical laboratory evaluations for the two controlled studies for patients who experience Grande 3 and 4 abnormalities by CTC criteria by treatment groups.

FDA Participants:

Victoria Tyson-Medlock
Rosemarie Neuner

Sponsor Attendees:

Jim Steck

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Telecon Record

Date:	**June 10, 2005**
Time:	**11:30 a.m.**
CDER Personnel:	**Victoria Tyson-Medlock** **Yuan (Richard) Chen**
Company Personnel:	**Jim Steck**
BLs:	**125057/45**

Dr. Richard Chen and I called Abbott and left a message requesting the following information:

- Two variables-country and site included in an ACRD file for both studies submitted to support this psoriatic arthritis supplement, M02-570 and M02-518.

Financial Disclosure by Clinical Investigators

Abbott Laboratories is submitting the following information under provisions of 21 CFR 54. Provided in this section are:

- Form FDA 3454 Certification: Financial Interests and Arrangements of Clinical Investigators covering Studies M02-518, M02-537 and M02-570 for investigators meeting the requirements of 21 CFR 54.2 (a) (b) and (f).
- Form FDA 3455 Disclosure: Financial Interests and Arrangements of Clinical Investigators for two investigators participating in covered studies M02-518 and its extension study M02-537.

This section is organized in the following manner:

Form FDA 3454

List of names of clinical investigators meeting the requirements of 21 CFR 54.2(a), (b) and (f)

Form FDA 3455

Details of each individual's disclosable financial arrangements, along with steps taken to minimize the potential bias of clinical study results.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Chris Ward	Vice President, Global Pharmaceutical Regulatory Affairs
FIRM / ORGANIZATION: Abbott Laboratories	
SIGNATURE: Ch Ward	DATE: 11/22/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

PI / Sub-Investigators

Antoni, Christian
(b) (6)

Atkins, Christopher
(b) (6)

Bacha, David
(b) (6)

Baumgartner, Scott W.
(b) (6)

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's [redacted] have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Beaulieu, Andre'
(b) (6)

Bensen, William George
(b) (6)

Bingham, Clifton
(b) (6)

Birbara, Charles
(b) (6)

Bombardieri, Stefano
(b) (6)

Burmester, Gerd
(b) (6)

Principal investigators (Pis) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Choy, Ernest

(b) (6)

Cividino, Alfred

(b) (6)

Combe, Bernard

(b) (6)

Dougados, Maxime

(b) (6)

Edwards, William

(b) (6)

Emery, Paul

(b) (6)

Ettlinger, Robert

(b) (6)

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Eyanson, Steven
(b) (6)

Fiechtner, Justus J.
(b) (6)

Fiocco, Guy
(b) (6)

Franklin, Michael
(b) (6)

Furie, Richard
(b) (6)

Gaylis, Norman B.
(b) (6)

Genovese, Mark C.
(b) (6)

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

(b) (6)

Gladman, Dafna

(b) (6)

Goupile, Philippe

(b) (6)

Greenwald, Maria

(b) (6)

Haraoui, Boulos

(b) (6)

Hein, Gert

(b) (6)

Principal investigators (Pis) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Helfgott, Simon
(b) (6)

Hitchon, Carol
(b) (6)

Kaltzwasser, Joachim Peter
(b) (6)

Kavanaugh, Arthur
(b) (6)

Subinvestigators under (b) (6)
(b) (6)
(b) (6)

Khraishi, Majed
(b) (6)

Kirkham, Bruce
(b) (6)

Principal investigators (Pis) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

(b) (6)

Mease, Philip

(b) (6)

Moliter, Jerry

(b) (6)

Neiman, Richard

(b) (6)

Rapoport, Ronald

(b) (6)

Ritchlin, Christopher

(b) (6)

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's [redacted] have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under [redacted] (b) (6) [redacted] meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

(b) (6)

Kivitz, Alan J.

(b) (6)

Klinkoff, Alice

(b) (6)

Koller, Marcus

(b) (6)

Ludivico, Charles

(b) (6)

Malaise, Michael

(b) (6)

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b) (6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b) (6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Subinvestigators under (b) (6)
(b) (6)

Sayers, Michael E.
(b) (6)

Schlosstein, Lee H.
(b) (6)

Solomon, Sheldon
(b) (6)

Starr, Michael
(b) (6)

Steinfeld, Serge
(b)(6)
(b)(6)
(b)(6)

Sutton, Evelyn D.

Principal investigators (PIs) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b)(6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b)(6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

(b) (6)

Thomson, Glen

(b)(6)

Thorne, J. Carter

(b) (6)

Tierney, Robert

(b) (6)

Tindall,Elizabeth

(b) (6)

Valente, Robert M.

(b) (6)

Veys, Eric

(b) (6)

Wallace, Daniel J.

(b)(6)

Principal investigators (Pis) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b)(6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b)(6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

List of Clinical Investigators from Studies M02-518, M02-537, and M02-570
Meeting the requirements of 21 CFR 54.2 (a) (b) and (f)

Welborne, Frank

(b) (6)

Wolfe, Frederick

(b)(6)

Wordsworth, Bryan Paul

(b)(6)

Principal investigators (Pis) appear in bold on this list; subinvestigators are in regular print. Note that PI's (b)(6) have disclosable financial arrangements described on FDA Form 3455, however, all subinvestigators under (b)(6) meet the requirements of 21 CFR 54.2 (a) (b) and (f).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) _____, who participated as a clinical investigator in the submitted study M02-518 (and its extension study M02-537) _____, is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Chris Ward	Vice President, Global Pharmaceutical Regulatory Affairs
FIRM / ORGANIZATION: Abbott Laboratories	
SIGNATURE: Chris Ward	DATE: 11/22/04

Paperwork Reduction Act Statement

Study M02-518 (and extension study M02-537)

Disclosure Financial Interest and Arrangements of Clinical Investigators

(b) (6) **Principal Investigator**

As provided in Form FDA 3455, the above-referenced investigator received significant payments from Abbott other than payments for conducting the above clinical studies. Details of (b)(6) disclosable financial arrangements and interest are summarized below, along with a description of the steps taken to minimize the potential bias of study results.

Summary

(b) (6) has received significant payments from Abbott after February 2, 1999 for consulting, honoraria for lectures, and clinical trial payments other than payments for the above clinical trials that total approximately $30,000. As principal investigator at his site, (b) (6) is responsible for the conduct of the clinical trial in compliance with 21 CFR 312.60

Steps taken to minimize the potential bias of the clinical study results:

The pivotal clinical trial M02-518 was a randomized, double-blind, placebo-controlled trial designed to limit sources of bias in general. In addition, a qualified independent assessor, other than the principal investigator, assessed key efficacy variables in the study (swollen joint count and tender joint count). An independent central laboratory assayed laboratory parameters measured in the study.

Finally, a subgroup statistical analysis of the primary efficacy endpoint (ACR 20 response) in Study M02-518 was carried out excluding the two study sites with financial interest. This analysis showed that when the sites with financial interest (b) (6) (b) (6) were excluded, the ACR 20 responses did not differ from those obtained in the full study population.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6) _____, who participated as a clinical investigator in the submitted study M02-518 (and its extension study M02-537) _____, is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Chris Ward	Vice President, Global Pharmaceutical Regulatory Affairs
FIRM / ORGANIZATION: Abbott Laboratories	
SIGNATURE: Chris Ward	DATE: 11.22.04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Study M02-518 (and extension study M02-537)

Disclosure Financial Interest and Arrangements of Clinical Investigators

[redacted] **Principal Investigator**

As provided in Form FDA 3455, the above-referenced investigator received significant payments from Abbott other than payments for conducting the above clinical studies. Details of [redacted] disclosable financial arrangements and interest are summarized below, along with a description of the steps taken to minimize the potential bias of study results.

Summary

[redacted] has received significant payments from Abbott after February 2, 1999 for payments other than payments for the above clinical trials that total approximately $40,000. This payment was in the form of a grant to [redacted] University given January 2003, partly in [redacted] name, to help fund an interdisciplinary education program in immune-mediated diseases. As principal investigator at his site, [redacted] is responsible for the conduct of the clinical trial in compliance with 21 CFR 312.60

Steps taken to minimize the potential bias of the clinical study results:

The pivotal clinical trial M02-518 was a randomized, double-blind, placebo-controlled trial designed to limit sources of bias in general. In addition, a qualified independent assessor, other than the principal investigator, assessed key efficacy variables in the study (swollen joint count and tender joint count). An independent central laboratory assayed laboratory parameters measured in the study.

Finally, a subgroup statistical analysis of the primary efficacy endpoint (ACR 20 response) in Study M02-518 was carried out excluding the two study sites with financial interest. This analysis showed that when the sites with financial interest [redacted] were excluded, the ACR 20 responses did not differ from those obtained in the full study population.

Certification Requirement
For Approval of a Drug Product
Concerning Using Services of Debarred Persons

- DEBARMENT STATEMENT -

Any application for approval of a new drug product submitted on or after June 1, 1992, per FD&C Act Section 306 (k)(1), must include:

> (1) A certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

Abbott Laboratories certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)].

James D. Steck
Director, Global Pharmaceutical Regulatory Affairs
Abbott Laboratories