CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103795 / S-5097

Trade Name: **Enbrel**

Generic Name: **Etanercept**

Sponsor: **Immunex Corporation**

Approval Date: **July 24, 2003**

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103795 / S-5097

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APPLICATION NUMBER:

103795 / S-5097

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103795/5097

JUL 24 2003

Immunex Corporation
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center Drive
Mail Stop 24-2-C
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Your request to supplement your biologics license application for Etanercept to expand the rheumatoid arthritis indication to include improving physical function has been approved.

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

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have submitted data to support such claims to us and had them approved.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

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

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

Sincerely,

(b)(6)

Patricia Keegan, M.D.
Acting Director
Division of Clinical Trials Design and Analysis
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

Enclosures: Final Draft Package Insert
Final Draft Patient Information Insert

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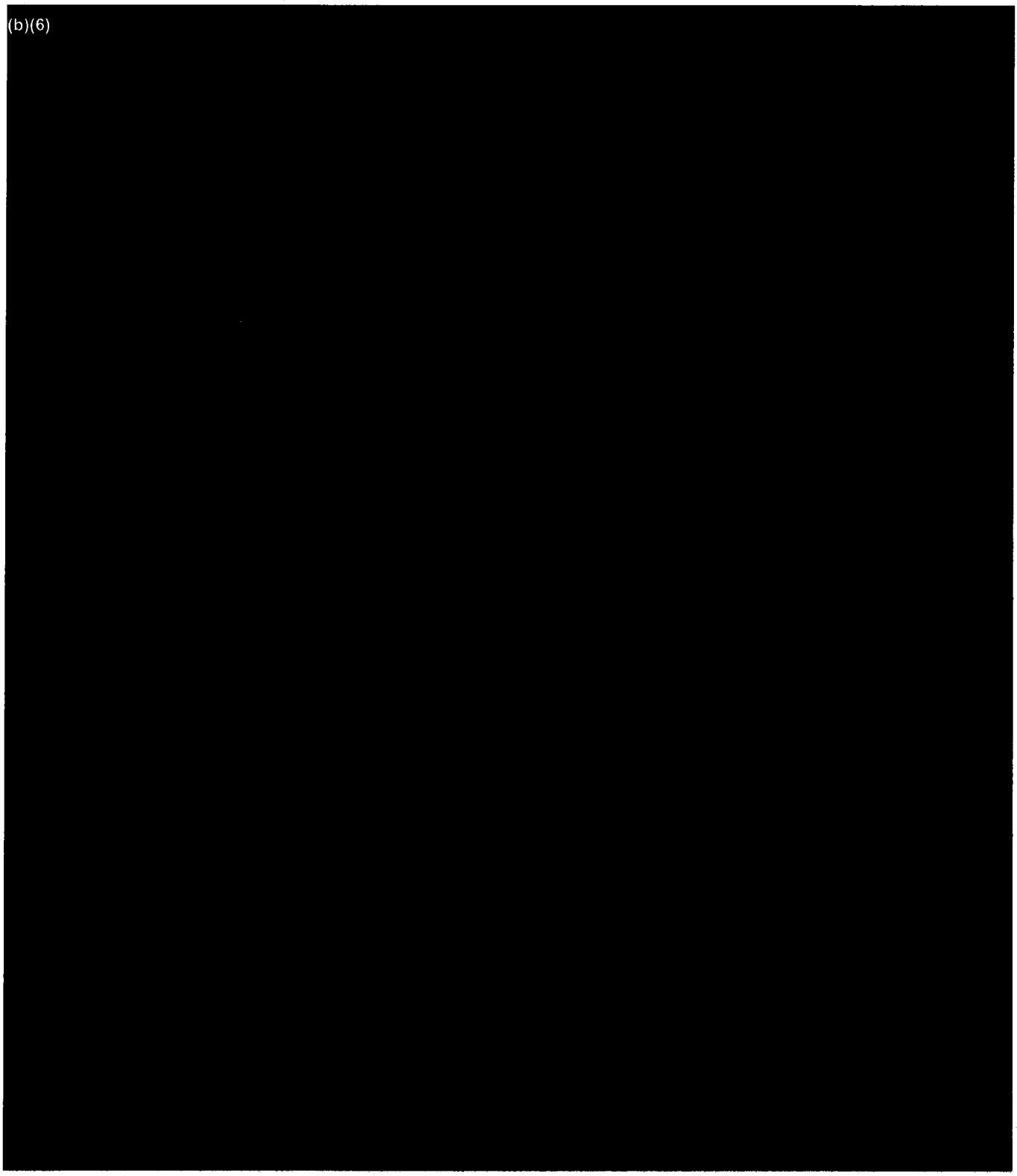

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CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

ENBREL®
(etanercept)

DESCRIPTION

ENBREL® (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ENBREL® is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection (BWFI), USP (containing 0.9% benzyl alcohol). Reconstitution with the supplied BWFI yields a multiple-use, clear, and colorless solution of ENBREL® with a pH of 7.4 ± 0.3. Each vial of ENBREL® contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

CLINICAL PHARMACOLOGY

General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and ankylosing spondylitis and the resulting joint pathology. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, psoriatic arthritis and ankylosing spondylitis (AS).[1, 2, 3, 4, 5, 6]

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms.[7] Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.[8, 9]

Etanercept inhibits binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive.[9] Cells expressing transmembrane TNF that bind ENBREL® are not lysed in vitro in the presence or absence of complement.[9]

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).[9]

Pharmacokinetics

After administration of 25 mg of ENBREL® by a single subcutaneous (SC) injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (Cmax) of 1.1 ± 0.6 mcg/mL and time to Cmax of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean Cmax was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a two- to seven-fold increase in peak serum concentrations and approximately four-fold increase in $AUC_{0\text{-}72\ hr}$ (range 1 to 17 fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on ENBREL® disposition or potential interactions with methotrexate.

Patients with JRA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL® twice weekly for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggests that the clearance of ENBREL® is reduced slightly in children ages 4 to 8 years. The pharmacokinetics of ENBREL® in children < 4 years of age have not been studied.

CLINICAL STUDIES

Adult Rheumatoid Arthritis

The safety and efficacy of ENBREL® were assessed in three randomized, double-blind, controlled studies. Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g., hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL® or placebo were

administered SC twice a week for 6 consecutive months. Results from patients receiving 25 mg are presented in Table 1.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that subjects in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/week) for at least 4 weeks and they had at least 6 tender or painful joints. Subjects in Study II received a dose of 25 mg ENBREL® or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of ENBREL® to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA; had never received treatment with MTX; and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL® were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg ENBREL®. Results from patients receiving 25 mg are presented in Table 1. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or ENBREL® doses, respectively.

The results of all three trials were expressed in percentage of patients with improvement in RA using American College of Rheumatology (ACR) response criteria.[10]

Clinical Response

The percent of ENBREL®-treated patients achieving ACR 20, 50, and 70 responses was consistent across all three trials. The results of the three trials are summarized in Table 1.

Table 1
ACR Responses in Placebo- and Active-Controlled Trials
(Percent of Patients)

	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo	ENBREL®[a]	MTX/ Placebo	MTX/ ENBREL®[a]	MTX	ENBREL®[a]
Response	N = 80	N = 78	N = 30	N = 59	N = 217	N = 207
ACR 20						
Month 3	23%	62%[b]	33%	66%[b]	56%	62%
Month 6	11%	59%[b]	27%	71%[b]	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%[b]	0%	42%[b]	24%	29%
Month 6	5%	40%[b]	3%	39%[b]	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%[b]	0%	15%[b]	7%	13%[c]
Month 6	1%	15%[b]	0%	15%[b]	14%	21%[c]
Month 12	NA	NA	NA	NA	22%	25%

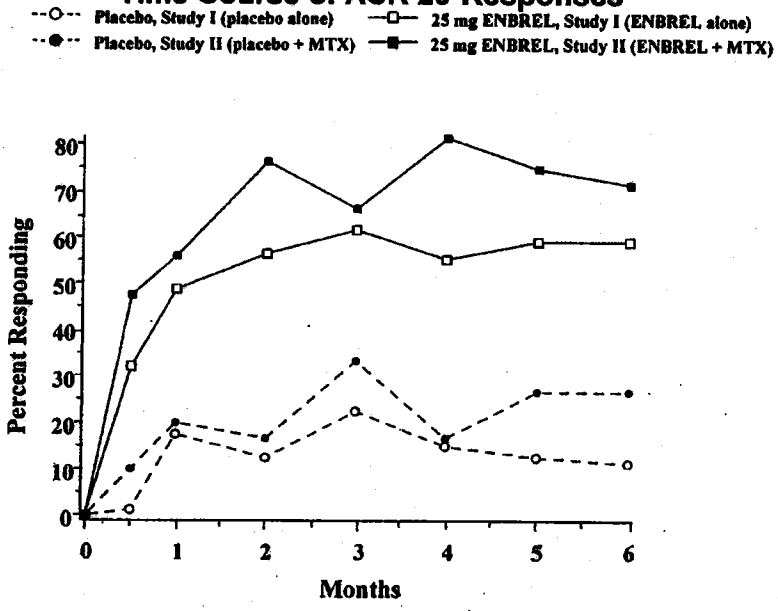
[a] 25 mg ENBREL® SC twice weekly.

[b] $p < 0.01$, ENBREL® vs. placebo.

[c] $p < 0.05$, ENBREL® vs. MTX.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg ENBREL® in Studies I and II is summarized in Figure 1. The time course of responses to ENBREL® in Study III was similar.

Figure 1
Time Course of ACR 20 Responses



Among patients receiving ENBREL®, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg ENBREL® was more effective than 10 mg (10 mg was not evaluated in Study II). ENBREL® was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of ENBREL® therapy. Over the 2-year study, 23% of ENBREL® patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in Table 2. Similar results were observed for ENBREL®-treated patients in Studies II and III.

Table 2
Components of ACR Response in Study I

Parameter (median)	Placebo N = 80		ENBREL®[a] N = 78	
	Baseline	3 Months	Baseline	3 Months*
Number of tender joints [b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints [c]	24.0	22.0	23.5	12.6[f]
Physician global assessment [d]	7.0	6.5	7.0	3.0[f]
Patient global assessment [d]	7.0	7.0	7.0	3.0[f]
Pain [d]	6.9	6.6	6.9	2.4[f]
Disability index [e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

* Results at 6 months showed similar improvement.

[a] 25 mg ENBREL® SC twice weekly.

[b] Scale 0-71.

[c] Scale 0-68.

[d] Visual analog scale; 0 = best, 10 = worst.

[e] Health Assessment Questionnaire[11]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f] $p < 0.01$, ENBREL® vs. placebo, based on mean percent change from baseline.

After discontinuation of ENBREL®, symptoms of arthritis generally returned within a month. Reintroduction of treatment with ENBREL® after discontinuations of up to 18 months resulted in the same magnitudes of response as patients who received ENBREL® without interruption of therapy based on results of open-label studies.

Continued durable responses have been seen for up to 36 months in open-label extension treatment trials when patients received ENBREL® without interruption. Some patients receiving ENBREL® for up to 3 years have been able to dose reduce and even discontinue concomitant steroids and/or methotrexate while maintaining a clinical response.

A Health Assessment Questionnaire (HAQ),[11] which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during Studies I and III. All subdomains of the HAQ were improved in patients treated with ENBREL®.

In Study III, health outcome measures were assessed by the SF-36 questionnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).[12] At 12 months, patients treated with 25 mg ENBREL® showed significantly more improvement in the PCS compared to the 10 mg ENBREL® group, but not in the MCS. Improvement in the PCS was maintained over the 24 months of ENBREL® therapy.

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either ENBREL® alone or the combination of ENBREL® and anakinra. The ACR_{50} response rate was 31% for patients treated with the combination of ENBREL® and anakinra and 41% for patients treated with ENBREL® alone, indicating no added clinical benefit of the combination over ENBREL® alone. Serious infections were increased with the combination compared to ENBREL® alone (see **WARNINGS**).

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the HAQ.[11] Additionally, in Study III, patients were administered the SF-36[12] Health Survey. In Studies I and II, patients treated with 25 mg ENBREL® twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg ENBREL® group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the ENBREL®/MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg ENBREL® twice weekly.

In Study III, patients treated with 25 mg ENBREL® twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to ENBREL® 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label ENBREL® studies, improvements in physical function and disability measures have been maintained for up to 4 years.

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. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 3. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

Table 3
Mean Radiographic Change Over 6 and 12 Months in Study III

		MTX	25 mg ENBREL®	MTX-ENBREL® (95% Confidence Interval*)	P-value
12 Months	Total Sharp score	1.59	1.00	0.59 (-0.12, 1.30)	0.110
	Erosion score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN score	0.56	0.52	0.04 (-0.39, 0.46)	0.529
6 Months	Total Sharp score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN score	0.38	0.27	0.11 (-0.14, 0.35)	0.585

* 95% confidence intervals for the differences in change scores between MTX and ENBREL®

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg ENBREL® group, and in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 69% of the original patients treated with 25 mg ENBREL® have been evaluated radiographically at 3 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 58% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with ENBREL®.

Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of ENBREL® were assessed in a two-part study in 69 children with polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 years with moderately to severely active polyarticular-course JRA refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) ENBREL® SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on ENBREL® or receive placebo for four months and assessed for disease flare. Responses were measured using the JRA Definition of Improvement (DOI),[13] defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of the six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.[14] In part 2, 6 of 25 (24%) patients remaining on ENBREL® experienced a

disease flare compared to 20 of 26 (77%) patients receiving placebo (p = 0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who received ENBREL® and 28 days for patients who received placebo. Each component of the JRA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on ENBREL®. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on ENBREL® continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JRA patients who developed a disease flare in part 2 and reintroduced ENBREL® treatment up to 4 months after discontinuation re-responded to ENBREL® therapy in open-label studies. Most of the responding patients who continued ENBREL® therapy without interruption have maintained responses for up to 18 months.

Studies have not been done in patients with polyarticular-course JRA to assess the effects of continued ENBREL® therapy in patients who do not respond within 3 months of initiating ENBREL® therapy, or to assess the combination of ENBREL® with methotrexate.

Psoriatic Arthritis

The safety and efficacy of ENBREL® were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement (N = 104); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; N = 173); (3) arthritis mutilans (N = 3); (4) asymmetric psoriatic arthritis (N = 81); or (5) ankylosing spondylitis-like (N = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients currently on MTX therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg ENBREL® or placebo were administered SC twice a week for 6 months.

Compared to placebo, treatment with ENBREL® resulted in significant improvements in measures of disease activity (Table 4).

Table 4

Components of Disease Activity in Psoriatic Arthritis

	Placebo N = 104		ENBREL®[a] N = 101	
Parameter (median)	Baseline	6 Months	Baseline	6 Months
Number of tender joints [b]	17.0	13.0	18.0	5.0
Number of swollen joints [c]	12.5	9.5	13.0	5.0
Physician global assessment [d]	3.0	3.0	3.0	1.0
Patient global assessment [d]	3.0	3.0	3.0	1.0
Morning stiffness (minutes)	60	60	60	15
Pain [d]	3.0	3.0	3.0	1.0
Disability index [e]	1.0	0.9	1.1	0.3
CRP (mg/dL) [f]	1.1	1.1	1.6	0.2

[a] $p < 0.001$ for all comparisons between ENBREL® and placebo at 6 months.

[b] Scale 0-78.

[c] Scale 0-76.

[d] Likert scale; 0 = best, 5 = worst.

[e] Health Assessment Questionnaire[11]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f] Normal range: 0 - 0.79 mg/dL

Among patients with psoriatic arthritis who received ENBREL®, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving ENBREL®, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. 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. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis.[15]

The skin lesions of psoriasis were also improved with ENBREL®, relative to placebo, as measured by percentages of patients achieving improvements in the psoriasis area and severity index (PASI).[16] Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the ENBREL® group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline.

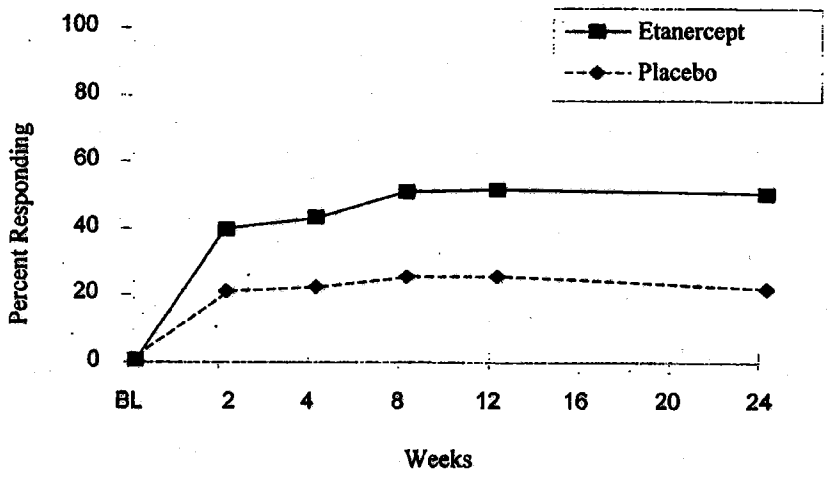
Ankylosing Spondylitis

The safety and efficacy of ENBREL® were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active ankylosing spondylitis. Patients were

between 18 and 70 years of age and had ankylosing spondylitis as defined by the modified New York Criteria for Ankylosing Spondylitis.[17] Patients were to have evidence of active disease based on values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and 2 of the following 3 other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study. Doses of 25 mg ENBREL® or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria.[18] Compared to placebo, treatment with ENBREL® resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 5).

Figure 2: ASAS 20 Responses in Ankylosing Spondylitis



At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving ENBREL®, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, ENBREL® vs. placebo). Similar responses were seen at week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multi-center, randomized, placebo-controlled study of 84 patients with ankylosing spondylitis.

Table 5

Components of Ankylosing Spondylitis Disease Activity

	Placebo N = 139		ENBREL®[a] N = 138	
Mean values at time points	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment[b]	63	56	63	36
Back pain[c]	62	56	60	34
BASFI[d]	56	55	52	36
Inflammation[e]	64	57	61	33
Acute phase reactants				
CRP (mg/dL)[f]	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

[a] $p < 0.0015$ for all comparisons between ENBREL® and placebo at 6 months. P-values for continuous endpoints were based on percent change from baseline.

[b] Measured on a Visual Analog Scale (VAS) scale with 0 = "none" and 100 = "severe."

[c] Average of total nocturnal and back pain scores, measured on a VAS scale with 0 = "no pain" and 100 = "most severe pain."

[d] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

[e] Inflammation represented by the average of the last 2 questions on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

[f] C-reactive protein (CRP) normal range: 0 - 1.0 mg/dL.

INDICATIONS AND USAGE

ENBREL® is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. ENBREL® can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL® is indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs.

ENBREL® is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. ENBREL® can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

CONTRAINDICATIONS

ENBREL® should not be administered to patients with sepsis or with known hypersensitivity to ENBREL® or any of its components.

WARNINGS

INFECTIONS

IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL®. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ENBREL®. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL® SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL® SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ENBREL® SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL® IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see PRECAUTIONS and ADVERSE REACTIONS: Infections).

IN A 24-WEEK STUDY OF CONCURRENT ENBREL® AND ANAKINRA THERAPY, THE RATE OF SERIOUS INFECTIONS IN THE COMBINATION ARM (7%) WAS HIGHER THAN WITH ENBREL® ALONE (0%). THE COMBINATION OF ENBREL® AND ANAKINRA DID NOT RESULT IN HIGHER ACR RESPONSE RATES COMPARED TO ENBREL® ALONE (see CLINICAL STUDIES: Clinical Response and ADVERSE REACTIONS: Infections).

Neurologic Events

Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL® therapy. The causal relationship to ENBREL® therapy remains unclear.

While no clinical trials have been performed evaluating ENBREL® therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.[19, 20] Prescribers should exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

Hematologic Events

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ENBREL®. The causal relationship to ENBREL® therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL® who have a previous history of significant hematologic abnormalities. 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 ENBREL®. Discontinuation of ENBREL® therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10^9/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

PRECAUTIONS

General

Allergic reactions associated with administration of ENBREL® during clinical trials have been reported in < 2% of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ENBREL® should be discontinued immediately and appropriate therapy initiated.

Information for Patients

If a patient or caregiver is to administer ENBREL®, the patient or caregiver should be instructed in injection techniques and how to measure the correct dose to help ensure the proper administration of ENBREL® (see the ENBREL® (etanercept) "Patient Information" insert). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles and syringes should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

Patients with Heart Failure

Two large clinical trials evaluating the use of ENBREL® in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with ENBREL® compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL® (see **ADVERSE REACTIONS: Patients with Heart Failure**). There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL®. There have also been rare reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using ENBREL® in patients who also have heart failure, and monitor patients carefully.

Immunosuppression

Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL®, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL® 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 ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving ENBREL® were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL®. The clinical significance of this is unknown. Patients receiving ENBREL® may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL® (see **PRECAUTIONS: Immunosuppression**).

It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL® therapy. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL® therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with ENBREL® may result in the formation of autoantibodies (see **ADVERSE REACTIONS: Autoantibodies**) and, rarely, in the development of a lupus-like syndrome (see **ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports**) which may resolve following withdrawal of ENBREL®. If a patient develops symptoms and findings suggestive of a lupus-like syndrome following treatment with ENBREL®, treatment should be discontinued and the patient should be carefully evaluated.

Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL®. However, in a study in which patients with active RA were treated for up to 24 weeks with concurrent ENBREL® and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with ENBREL® alone (0%) (see also **WARNINGS**). Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10^9/L).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL® or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

Pregnancy (Category B)

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL®. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether ENBREL® 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 ENBREL®, a decision should be made whether to discontinue nursing or to discontinue the drug.

Geriatric Use

A total of 197 RA patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and

younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

ENBREL® is indicated for treatment of polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. For issues relevant to pediatric patients, in addition to other sections of the label, see also **WARNINGS; PRECAUTIONS: Immunizations;** and **ADVERSE REACTIONS: Adverse Reactions in Patients with JRA.** ENBREL® has not been studied in children < 4 years of age.

ADVERSE REACTIONS

Adverse Reactions in Adult Patients with RA, Psoriatic Arthritis, or Ankylosing Spondylitis

ENBREL® has been studied in 1440 patients with RA, followed for up to 57 months, in 157 patients with psoriatic arthritis for 6 months, and in 222 patients with ankylosing spondylitis for up to 10 months. In controlled trials, the proportion of ENBREL®-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied. The vast majority of these patients were treated with the recommended dose of 25 mg SC twice weekly.

Injection Site Reactions

In controlled trials, approximately 37% of patients treated with ENBREL® developed injection site reactions. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given. In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with ENBREL® therapy.

Infections

In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis, and ankylosing spondylitis patients treated with ENBREL® and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL®- and placebo-treated patients.

In placebo-controlled trials in RA, psoriatic arthritis, and ankylosing spondylitis no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and ENBREL®-treated groups). In all clinical trials in RA, serious infections

experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in ENBREL®- and placebo-treated patients from controlled trials. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL®. Some have occurred within a few weeks after initiating treatment with ENBREL®. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL® treatment may increase mortality in patients with established sepsis.[21]

In patients who received both ENBREL® and anakinra for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

In post-marketing 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 ENBREL® alone or in combination with immunosuppressive agents.

Malignancies

Patients have been observed in clinical trials with ENBREL® for over 3 years. The incidence of malignancies has not increased with extended exposure to ENBREL® and is similar to that expected when projected from the National Cancer Institute's Surveillance, Epidemiology and End Results database.[22]

Immunogenicity

Patients with RA, psoriatic arthritis, or ankylosing spondylitis were tested at multiple timepoints for antibodies to ENBREL®. Antibodies to the TNF receptor portion or other protein components of the ENBREL® drug product, all non-neutralizing, were detected at least once in sera of $< 5\%$ of adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. No apparent correlation of antibody development to clinical response or adverse events was observed. Results from JRA patients were similar to those seen in adult RA patients treated with ENBREL®. The long-term immunogenicity of ENBREL® is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ENBREL® 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, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of

antibodies to ENBREL® with the incidence of antibodies to other products may be misleading.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple timepoints. In Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who developed new positive ANA (titer ≥1:40) was higher in patients treated with ENBREL® (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL® compared to 4% of placebo-treated patients) and by crithidia luciliae assay (3% of patients treated with ENBREL® compared to none of placebo-treated patients). The proportion of patients treated with ENBREL® who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no pattern of increased autoantibody development was seen in ENBREL® patients compared to MTX patients.

The impact of long-term treatment with ENBREL® on the development of autoimmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome.

Other Adverse Reactions

Table 6 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL® compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III. Adverse events in psoriatic arthritis and ankylosing spondylitis trials were similar to those reported in RA clinical trials.

Table 6
Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
Event	Placebo† (N = 152)	ENBREL® (N = 349)	MTX (N = 217)	ENBREL® (N = 415)
Injection site reaction	10	37	7	34
Infection (total)**	32	35	72	64
Non-upper respiratory infection (non-URI)**	32	38	60	51
Upper respiratory infection (URI)**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	-	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	-	-	2	0

* Includes data from the 6-month study in which patients received concurrent MTX therapy.

† The duration of exposure for patients receiving placebo was less than the ENBREL®-treated patients.

** Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL® N = 213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among ENBREL®- and control-treated patients. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL®, malignancies (see **ADVERSE REACTIONS: Malignancies**) and infections (see **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, and ankylosing spondylitis clinical trials are listed by body system below:

Cardiovascular:	heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis
Digestive:	cholecystitis, pancreatitis, gastrointestinal hemorrhage
Musculoskeletal:	bursitis, polymyositis
Nervous:	cerebral ischemia, depression, multiple sclerosis (see **WARNINGS**)
Respiratory:	dyspnea, pulmonary embolism
Urogenital:	membranous glomerulonephropathy

In a randomized controlled trial in which 51 patients with RA received ENBREL® 50 mg twice weekly and 25 patients received ENBREL® 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

Adverse Reactions in Patients with JRA

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see **WARNINGS** and other sections under **ADVERSE REACTIONS**). Differences from adults and other special considerations are discussed in the following paragraphs.

Severe adverse reactions reported in 69 JRA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS: Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

Forty-three of 69 (62%) children with JRA experienced an infection while receiving ENBREL® during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

The following adverse events were reported more commonly in 69 JRA patients receiving 3 months of ENBREL® compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).

In post-marketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see **WARNINGS**), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to ENBREL® therapy are unknown.

Patients with Heart Failure

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either ENBREL® 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either ENBREL® 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with ENBREL® at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL® (see **PRECAUTIONS: Patients with Heart Failure**).

Adverse Reaction Information from Spontaneous Reports

Adverse events have been reported during post-approval use of ENBREL®. 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 ENBREL® exposure.

Additional adverse events are listed by body system below:

Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular:	chest pain, vasodilation (flushing), new-onset congestive heart failure (see **PRECAUTIONS: Patients with Heart Failure**)
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)
Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
Nervous:	paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or

	isolated demyelinating conditions such as transverse myelitis or optic neuritis (see **WARNINGS**)
Ocular:	dry eyes, ocular inflammation
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

OVERDOSAGE

The maximum tolerated dose of ENBREL® has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of ENBREL®. Single IV doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

DOSAGE AND ADMINISTRATION

Adult Patients

The recommended dose of ENBREL® for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 25 mg given twice weekly as a subcutaneous injection 72-96 hours apart (see **CLINICAL STUDIES**). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL®. Based on a study of 50 mg ENBREL® twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than 25 mg twice weekly are not recommended (see **ADVERSE REACTIONS**).

JRA Patients

The recommended dose of ENBREL® for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly as a subcutaneous injection 72-96 hours apart. Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL®. Concurrent use with methotrexate and higher doses of ENBREL® have not been studied in pediatric patients.

Preparation of ENBREL®

ENBREL® is intended for use under the guidance and supervision of a physician. Patients may self-inject when deemed appropriate and if they receive medical follow-up,

as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose.

ENBREL® should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL®.

A vial adapter is supplied for use when reconstituting the lyophilized powder. However, the vial adapter should not be used if multiple doses are going to be withdrawn from the vial. If the vial will be used for multiple doses, a 25-gauge needle should be used for reconstituting and withdrawing ENBREL®, and the supplied "Mixing Date:" sticker should be attached to the vial and the date of reconstitution entered. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days.

If using the vial adapter, twist the vial adapter onto the diluent syringe. Then, place the vial adapter over the ENBREL® vial and insert the vial adapter into the vial stopper. Push down on the plunger to inject the diluent into the ENBREL® vial. Keeping the diluent syringe in place, gently swirl the contents of the ENBREL®vial during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

If using a 25-gauge needle to reconstitute and withdraw ENBREL®, the diluent should be injected very slowly into the ENBREL® vial. It is normal for some foaming to occur. The contents should be swirled gently during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

Generally, dissolution of ENBREL® takes less than 10 minutes. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains.

Withdraw the correct dose of reconstituted solution into the syringe. Some foam or bubbles may remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from the syringe. Attach a 27-gauge needle to inject ENBREL®.

The contents of one vial of ENBREL® solution should not be mixed with, or transferred into, the contents of another vial of ENBREL®. No other medications should be added to solutions containing ENBREL®, and do not reconstitute ENBREL® with other diluents. Do not filter reconstituted solution during preparation or administration.

The ENBREL® (etanercept) "Patient Information" insert contains more detailed instructions on the preparation of ENBREL®. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days. Discard reconstituted solution after 14 days. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.

Administration of ENBREL®

Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. See the ENBREL® (etanercept) "Patient Information" insert for detailed information on injection site selection and dose administration.

Storage and Stability

Do not use a dose tray beyond the expiration date stamped on the carton, dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL® (sterile powder) must be refrigerated at 2°-8°C (36°-46°F). DO NOT FREEZE.

Reconstituted solutions of ENBREL® prepared with the supplied Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol), using a 25-gauge needle, may be stored for up to 14 days if refrigerated at 2°-8°C (36°-46°F). Discard reconstituted solution after 14 days. **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

HOW SUPPLIED

ENBREL® is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½ inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four "Mixing Date:" stickers.

Rx Only

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AMGEN®

Wyeth®

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ENBREL®
(etanercept)

PATIENT INFORMATION

ENBREL® (pronounced en-brel)

Read these instructions carefully before you start taking ENBREL®. You should 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 medication and at check ups. Talk to your doctor if you have any questions about your treatment with ENBREL®.

What is ENBREL®?

ENBREL® is a medicine for adults and children with moderate to severe forms of rheumatoid arthritis (RA) and a type of disease called psoriatic (sore-ee-ah-tick) arthritis. ENBREL® is also for adults with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis) (AS). RA, psoriatic arthritis, and AS are inflammatory diseases that affect the joints in your body. Psoriatic arthritis is usually seen in patients with psoriasis, a skin condition that can also cause thick red or silvery skin patches ("psoriatic skin lesions") that can appear anywhere on the body.

How does ENBREL® work?

ENBREL® is a type of protein called a *TNF blocker* that blocks the action of a substance your body makes called TNF-alpha (tumor necrosis factor alpha). TNF-alpha is made by your body's immune system. People with immune diseases like RA and psoriatic arthritis, as well as patients with AS, have too much TNF-alpha in their bodies, which can cause inflammation and lead to painful, swollen joints and psoriatic skin lesions in psoriatic arthritis. ENBREL® can reduce the amount of TNF in the body to normal levels, helping to treat joint damage and skin lesions.

While taking ENBREL® can block the damage that too much TNF-alpha can cause, it can also lower the ability of your immune system to fight infections. So, taking ENBREL® can make you more prone to getting infections or make any infection that you may have worse.

What important information do I need to know about taking ENBREL®?

All medicines have side effects. Medicines, like ENBREL®, that affect your immune system can cause serious side effects. The possible serious side effects include:

Serious infections: There have been rare cases where patients taking ENBREL® or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi that have spread throughout their body (sepsis). Some patients have died from these infections. If you tend to get infections easily or if you develop an infection while taking ENBREL®, you should tell your doctor right away.

Nervous system diseases: There have been rare cases of disorders that affect the nervous system of people taking ENBREL® or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling throughout your body, problems with your vision, weakness in your arms and/or legs and dizziness.

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 your treatment. Some people have also had symptoms that resemble lupus (rash on your face and arms that gets worse in the sun) that may go away when you stop taking ENBREL®.

Heart problems: You should also tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on ENBREL®, or may want to monitor you more closely.

Allergic reactions: Some patients have had allergic reactions to ENBREL®. If you develop a severe rash, swollen face or difficulty breathing while taking ENBREL®, call your doctor right away.

There have also been very rare reports of cancer (malignancies) in patients taking ENBREL®. These reports do not appear to be different for people taking ENBREL®, as for those people in the general population who are not taking ENBREL®.

Before you start taking ENBREL® you should tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open cut or sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from ENBREL®. If you are unsure, please ask your doctor.
- A history of infections that keep coming back or other conditions, like diabetes, 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. You will need to be examined for TB and have a skin test.
- If you experience any numbness or tingling or have or have ever had a disease that affects your nervous system like multiple sclerosis.
- If you have been newly diagnosed or are being treated for congestive heart failure.
- 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 are the other more common side effects with ENBREL®?

- Reactions where the injection was given. These reactions are usually mild and included redness, rash, swelling, itching, or bruising. These usually go away within 3 to 5 days. If you have pain, redness or swelling around the injection site that doesn't go away or gets worse, call your doctor right away.
- Upper respiratory infections (sinus infections)
- Headaches

Who should not take ENBREL®?

You should not take ENBREL® if you have ever had an allergic reaction to ENBREL®.

Can I take ENBREL® if I am pregnant or breast-feeding?

ENBREL® 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 doctor if you are pregnant, become pregnant, or are thinking about becoming pregnant.

Can I take ENBREL® if I am taking other medicines for my RA, Psoriatic Arthritis, Ankylosing Spondylitis or other conditions?

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

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

How do I take ENBREL®?

ENBREL® is given by injection under the skin twice a week. The amount (one dose per vial or more than one dose per vial) of ENBREL® that your doctor will tell you to use is based on body weight.

Make sure you have been shown how to inject ENBREL® before you do it yourself. You can call your doctor or the ENBREL® toll-free information line at 1-888-4ENBREL (1-888-436-2735) if you have any questions about ENBREL® or about giving yourself or your child 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 ENBREL®?

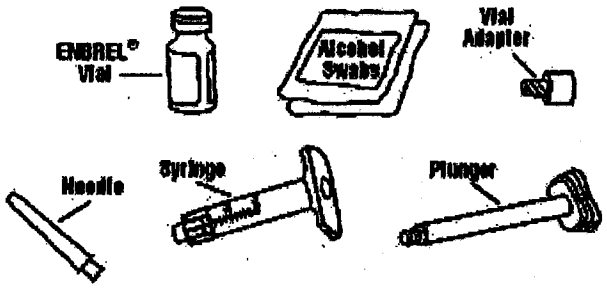
If you forget to take ENBREL® when you are supposed to, contact your doctor to find out when to take your next dose of ENBREL®.

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

STEP 1: Setting up for an Injection

1. Select a clean, well-lit, flat work surface, such as a table.
2. Take the ENBREL® dose tray out of the refrigerator and place it on your flat work surface.
3. Check the expiration date on the dose tray. If the expiration date has passed, do not use the dose tray. Also check to make sure the dose tray has seven items as pictured below:

   - One prefilled diluent syringe containing 1 mL of diluent (liquid)
   - One plunger
   - One ENBREL® vial
   - One 27-gauge ½ inch needle in hard plastic cover
   - One vial adapter
   - Two alcohol swabs



If the expiration date has passed or the seven items are not included in the dose tray, contact your pharmacist or call 1-888-4ENBREL (1-888-436-2735) for assistance.

4. Wash your hands with soap and warm water.

5. Peel the paper seal off the dose tray and remove all items.

6. Inspect the volume of diluent in the syringe with the gray tip cap pointing down. Use the unit markings on the side of the syringe to make sure there is at least 1 mL of liquid in the syringe. If the level of liquid is below the 1 mL mark, do not use. Call 1-888-4ENBREL (1-888-436-2735) for assistance.

STEP 2: Preparing the ENBREL® Solution

There are two methods for preparing the ENBREL® solution. For some children, one vial of ENBREL® solution can be used for more than one dose. The free-hand method should be used for children on ENBREL® who are using one vial of ENBREL® solution for more than one dose. **You should not use the vial adapter method if you will be using the vial more than once.** Ask your healthcare provider if you have questions about which method to use.

- **The Vial Adapter Method**

Adult patients and larger children on ENBREL® may use the vial adapter device to assist with mixing the powder with the liquid and withdrawing ENBREL®, and then use a 27-gauge needle to inject the dose. **This method should not be used for children using multiple doses from the same vial of ENBREL®.** The instructions for using the vial adapter method are in STEP 2A.

- **The Free-Hand Method**

In the free-hand method, a 25-gauge needle is used to assist with mixing the powder with the liquid and withdrawing ENBREL®, and a 27-gauge needle is used to inject the dose. Instructions for using the free-hand method are in STEP 2B.

The instructions for preparing additional doses from the same vial of ENBREL® solution are in STEP 3. For each additional dose, you will need two new needles (one 25-gauge

needle to withdraw the solution and one 27-gauge needle for injection) and one new empty syringe (1 mL). **NEVER REUSE A SYRINGE OR NEEDLE.**

If you are using the vial of ENBREL® for more than one dose, you should write the date you mixed the powder and liquid in the area marked "Mixing Date:" on the supplied sticker attached to these instructions, and attach the sticker to the ENBREL® vial.

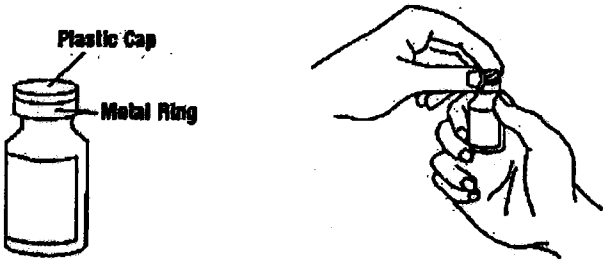
After you have withdrawn the dose of ENBREL® that you need, store the ENBREL® vial (in the dose tray) in the refrigerator at 36° to 46°F (2° to 8°C) as soon as possible, but always within 4 hours of mixing the solution.

The ENBREL® solution must be used within 14 days of the mixing date. You should discard the ENBREL® vial and any remaining solution if it is not used within 14 days. Do not mix any remaining liquid in one vial of ENBREL® solution with another.

There is a tool available which can help you remove the pink plastic cap on the ENBREL® vial, the gray tip cap on the prefilled diluent syringe and the needle cover on the syringe. This cap removal tool is provided to ENBREL® patients in the Resource Kit. You can request the Resource Kit by calling 1-888-4ENBREL (1-888-436-2735).

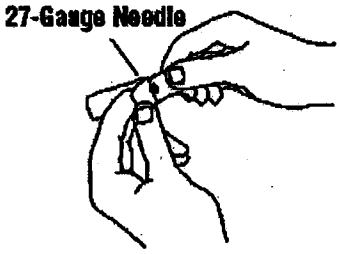
STEP 2A: Vial Adapter Method

1. Remove the pink plastic cap from the ENBREL® vial. Do not remove the gray stopper or silver metal ring around the top of the ENBREL® vial.

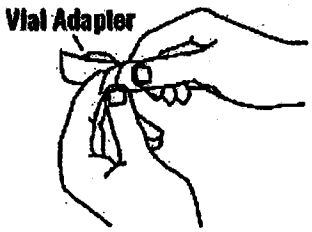


2. Place the ENBREL® vial on your flat work surface or turn your dose tray upside down and place your ENBREL® vial in the round space marked "V". Use one alcohol swab to clean the gray stopper on the ENBREL® vial. Do not touch the gray stopper with your hands.

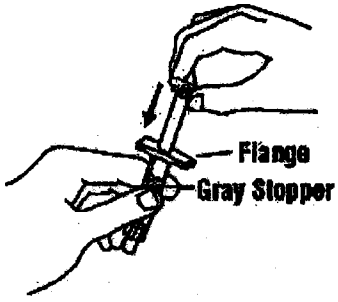
3. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use.



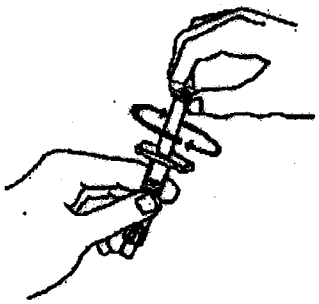
4. Open the wrapper that contains the vial adapter by peeling apart the tabs and set the vial adapter aside for later use. Do not touch the spike inside the vial adapter.



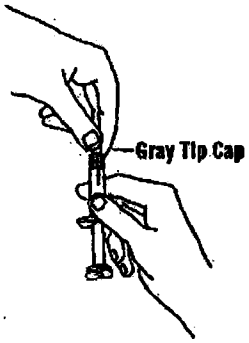
5. Slide the plunger into the flange end of the syringe.



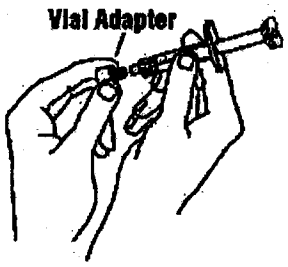
6. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger clockwise until a slight resistance is felt.



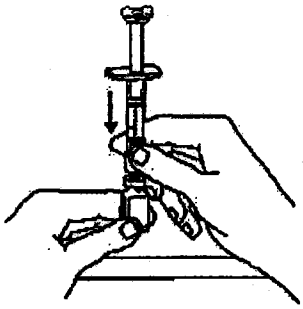
7. Remove the gray tip cap from the prefilled diluent syringe. Do not bump or touch the plunger. Doing so could cause the liquid to leak out. You may see a drop of liquid when removing the gray tip cap. This is normal. Place the gray tip cap on your flat work surface. Do not touch the syringe tip.



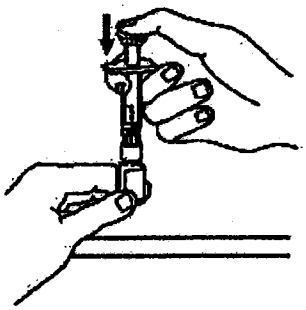
8. Once the gray tip cap is removed, pick up the vial adapter with your free hand. Twist the vial adapter onto the syringe until a slight resistance is felt. Do not over-tighten.



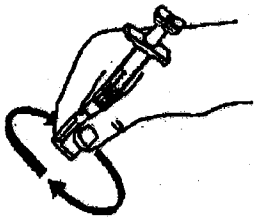
9. Hold the ENBREL® vial upright on your flat work surface. Grasp the sides of the vial adapter and place it over the top of the ENBREL® vial. Do not bump or touch the plunger. Doing so could cause the liquid to leak out. Insert the vial adapter into the gray stopper on the ENBREL® vial. The plastic spike inside the vial adapter should puncture the gray stopper. The vial adapter should fit snugly.



10. Hold the ENBREL® vial upright on your flat work surface and push the plunger down until all the liquid from the syringe is in the ENBREL® vial. You may see foaming (bubbles) in the vial. This is normal.

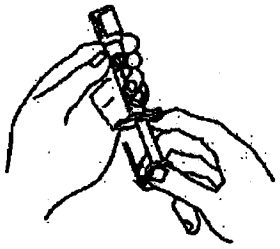


11. Gently swirl the ENBREL® vial in a circular motion to dissolve the powder. If you used the dose tray to hold your ENBREL® vial, take the vial (with the vial adapter and syringe still attached) out of the dose tray, and gently swirl the vial in a circular motion to dissolve the powder.



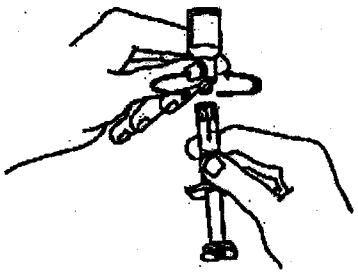
DO NOT SHAKE. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it is discolored, contains lumps, flakes, or particles.** If all the powder in the ENBREL® vial is not dissolved or there are particles present after 10 minutes, call 1-888-4ENBREL (1-888-436-2735) for assistance.

12. Turn the ENBREL® vial upside down. Hold the syringe at eye level and slowly pull the plunger down to the unit markings on the side of the syringe that correspond with your/your child's dose. For adult patients, remove the entire volume (1 mL), unless otherwise instructed by your doctor. Be careful not to pull the plunger completely out of the syringe. Some white foam may remain in the ENBREL® vial. This is normal.

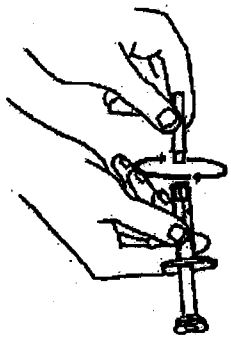


13. Check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the vial, slowly pull back on the plunger to again draw the correct amount of solution back into the syringe.

14. Remove the syringe from the vial adapter, by holding the vial adapter with one hand and turning the syringe counterclockwise with your other hand. Do not touch or bump the plunger. Place the ENBREL® vial with the vial adapter on your flat work surface.



15. Continue to hold the barrel of the syringe. With your free hand, twist the 27-gauge needle onto the tip of the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL®.

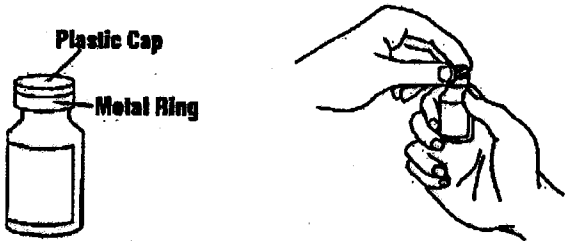


GO TO STEP 4: CHOOSING AND PREPARING AN INJECTION SITE.

STEP 2B: Free-Hand Method

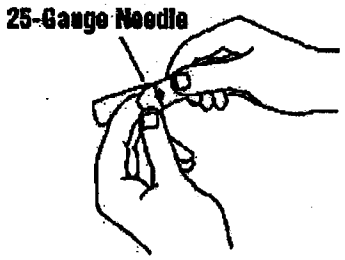
If you are preparing a dose from an ENBREL® vial that was previously used, go to STEP 3: Preparing Additional Doses from a Single ENBREL® Vial.

1. Remove the pink plastic cap from the ENBREL® vial. Do not remove the gray stopper or silver metal ring around the top of the ENBREL® vial. Write the date you mix the powder and solution on the supplied "Mixing Date:" sticker and attach it to the ENBREL® vial.

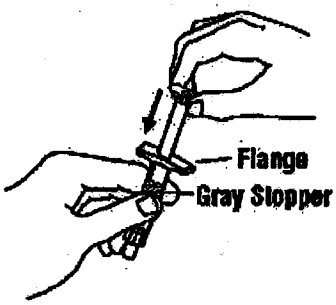


2. Place the ENBREL® vial on your flat work surface. Use one alcohol swab to clean the gray stopper on the ENBREL® vial. Do not touch the gray stopper with your hands.

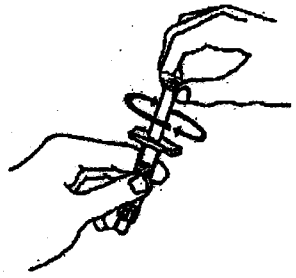
3. Open the wrapper that contains the 25-gauge needle by peeling apart the tabs and set the needle aside for later use. The 25-gauge needle will be used to mix the liquid with the powder and for withdrawing ENBREL® from the vial.



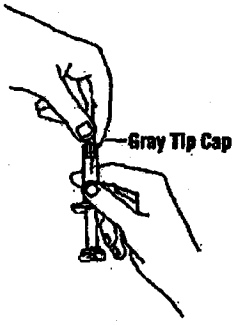
4. Slide the plunger into the flange end of the syringe.



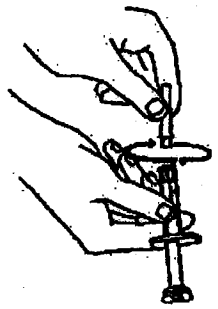
5. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger clockwise until a slight resistance is felt.



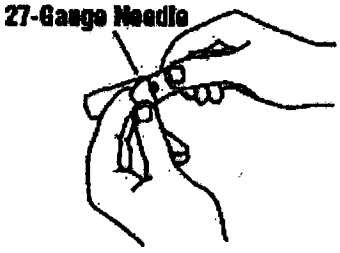
6. Remove the gray tip cap from the prefilled diluent syringe. Do not touch or bump the plunger. Doing so could cause the liquid to leak out. You may see a drop of liquid when removing the tip cap. This is normal. Place the gray tip cap on your flat work surface. Do not touch the syringe tip.



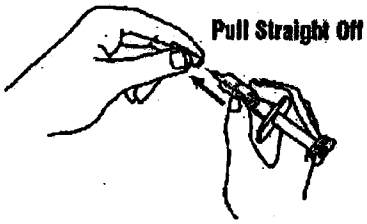
7. Continue to hold the barrel of the syringe. With your free hand, twist the 25-gauge needle onto the tip of the syringe until it fits snugly. Place the syringe on your flat work surface.



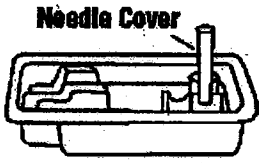
8. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use. The 27-gauge needle will be used to inject the dose.



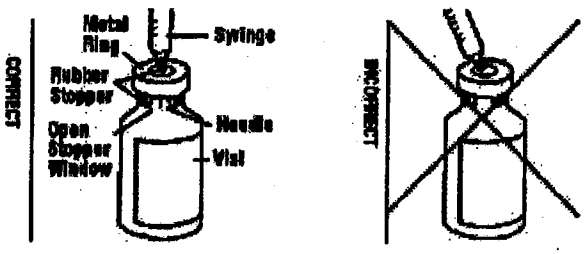
9. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with one hand, and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.



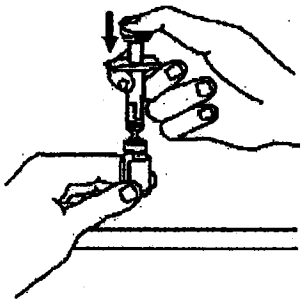
10. Place the needle cover (open side up) in the round space marked "N" in the ENBREL® dose tray.



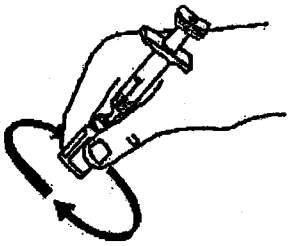
11. Place the ENBREL® vial on your flat work surface. Hold the syringe with the needle facing up, and gently pull back on the plunger to pull a small amount of air into the syringe. Then, insert the needle straight down through the center ring of the gray stopper (see illustrations). You should feel a slight resistance and then a "pop" as the needle goes through the center of the stopper. Look for the needle tip inside the open stopper window. If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no "pop". The needle may enter at an angle and bend, break or prevent you from adding diluent into the ENBREL® vial.



12. Push the plunger down VERY SLOWLY until all liquid from the syringe is in the ENBREL® vial. Adding the liquid too fast will cause foaming (bubbles).

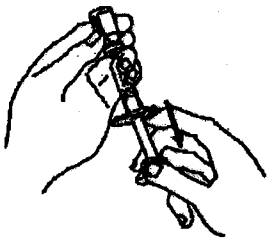


13. Leave the syringe in place. Gently swirl the ENBREL® vial in a circular motion to dissolve the powder.



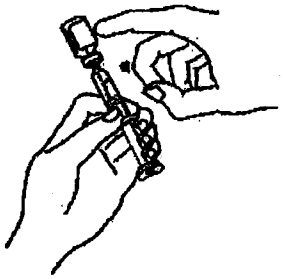
DO NOT SHAKE. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it is discolored, contains lumps, flakes, or particles.** If all the powder in the ENBREL® vial is not dissolved or there are particles present after 10 minutes, call 1-888-4ENBREL (1-888-436-2735) for assistance.

14. With the needle in the ENBREL® vial, turn the vial upside down. Hold the syringe at eye level and slowly pull the plunger down to the unit markings on the side of the syringe that correspond with your child's dose. Make sure to keep the tip of the needle in the solution. Some white foam may remain in the ENBREL® vial. This is normal.

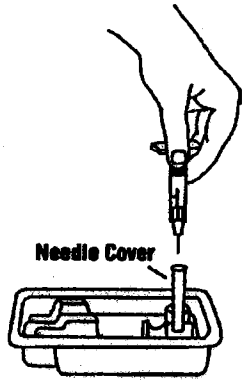


15. With the needle still inserted in the ENBREL® vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe.

Slowly push the plunger up to remove the air bubbles. If you push solution back into the vial, slowly pull back on the plunger to draw the correct amount of solution back into the syringe.

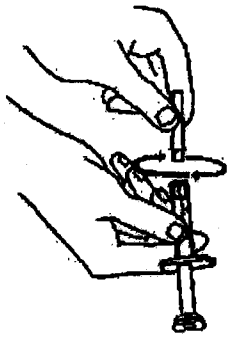


16. Remove the syringe and needle from the ENBREL® vial. Keep the needle attached to the syringe and insert the 25-gauge needle straight down into the needle cover in the ENBREL® dose tray.



You should hear a "snap" when the needle is secure in the needle cover. Once the needle is secure in the needle cover, untwist the 25-gauge needle from the syringe and dispose of the needle in your SHARPS container.

17. Twist the 27-gauge needle onto the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL®.



GO TO STEP 4: CHOOSING AND PREPARING AN INJECTION SITE.

STEP 3: Preparing Additional Doses from a Single ENBREL® Vial

1. Select a clean, well-lit, flat work surface, such as a table.

2. The needles and syringes supplied with ENBREL® should not be reused. You will need new ones for each additional dose. Your healthcare provider will tell you what type of syringes (1 mL) and needles (25- and 27-gauge) to use. Alcohol swabs are available at the drug store. Place the sterile syringe with a 25-gauge needle (for withdrawing ENBREL®), a 27-gauge needle (for injecting ENBREL®) and two alcohol swabs on your flat work surface.

3. Take the vial of ENBREL® solution that is stored in the dose tray out of the refrigerator and place it on your flat work surface.

4. Check the mixing date you wrote on the sticker on the ENBREL® vial. **Discard the ENBREL® vial if more than 14 days have passed since the ENBREL® solution was mixed.**

5. Wash your hands with soap and warm water.

6. Use one alcohol swab to clean the gray stopper on the ENBREL® vial. Do not touch the stopper with your hands.

7. If the syringe and the 25-gauge needle are not pre-assembled, assemble them as instructed by your healthcare provider.

8. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use. The 27-gauge needle will be used to inject the dose of ENBREL®.

9. Hold the syringe and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Place the needle cover (open side up) in the round space marked "N" in the ENBREL® dose tray.

10. Place the ENBREL® vial on your flat work surface. Hold the syringe with the needle facing up, and gently pull back the plunger to pull a small amount of air into the syringe. Then, insert the 25-gauge needle straight down through the center ring of the gray stopper. You should feel a slight resistance and then a "pop" as the needle goes through the center of the stopper. Look for the needle tip inside the open stopper window. If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no "pop". The needle may enter at an angle and bend, break, or prevent proper withdrawal of ENBREL® solution from the vial.

11. Keep the needle in the ENBREL® vial and turn the vial upside down. Hold the syringe at eye level, and slowly pull the plunger down to the unit markings on the syringe that correspond to your child's dose. As the amount of solution in the ENBREL® vial drops, you may need to pull the needle back just enough to keep the tip of the needle in the solution.

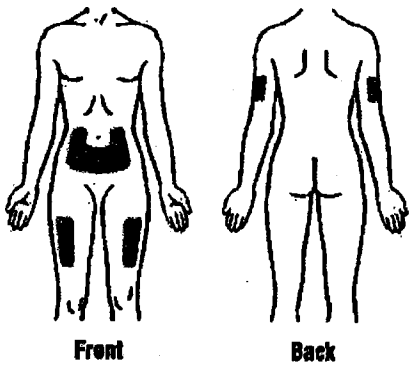
12. With the needle still inserted in the ENBREL® vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the ENBREL® vial, slowly pull back on the plunger to again draw the correct amount of solution back into the syringe.

13. Remove the syringe and needle from the ENBREL® vial. Keep the needle attached to the syringe and insert the 25-gauge needle straight down into the needle cover in the ENBREL® dose tray. You should hear a "snap" when the needle is secure in the needle cover. Once the needle is secure in the needle cover, remove the 25-gauge needle from the syringe and dispose of the needle in your SHARPS container.

14. Twist the 27-gauge needle onto the tip of the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL®.

STEP 4: Choosing and Preparing an Injection Site

1. Three recommended injection sites for ENBREL® include: (1) the front of the middle thighs; (2) the abdomen, except for the two-inch area right around the navel; and, (3) the outer area of the upper arms.

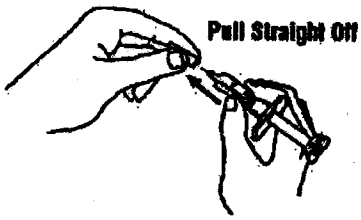


2. Rotate the site for each injection. Make sure that the new injection is given at least one inch from sites of recent injections. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

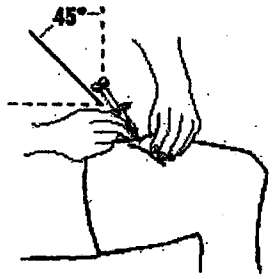
3. To prepare the area of skin where ENBREL® is to be injected, wipe the injection site with a new alcohol swab. **Do not touch this area again before giving the injection.**

STEP 5: Injecting the ENBREL® Solution

1. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with one hand and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

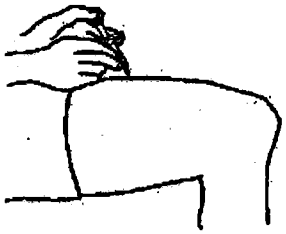


2. With one hand, gently pinch the cleaned area of skin and hold it firmly. With the other hand, hold the syringe (like a pencil) at a 45 degree angle to the skin.



3. With a quick, "dart-like" motion, push the needle into the skin.

4. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears in the syringe, slowly push the plunger all the way down to inject ENBREL®. If blood comes into the syringe, do not inject ENBREL® because the needle has entered a blood vessel. Withdraw the needle and repeat the steps to prepare for an injection. Do not use the same syringe and needle. Dispose of the used needle and syringe in your SHARPS container.



5. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted.

6. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

7. **FOR USE IN CHILDREN** - If there is enough solution left in the ENBREL® vial for another dose, refrigerate the ENBREL® vial (in the dose tray) after use. Otherwise, discard the ENBREL® vial and any remaining solution.

STEP 6: Disposing of Supplies

- The syringe, needles, and vial adapter should **NEVER** be reused. **NEVER** recap a needle.

- Dispose of both the used needle and syringe in a puncture-resistant container. A SHARPS container made specifically for disposing of used syringes and needles may be used. **Do not** recycle the container.

- Keep the container out of the reach of children. When the container is about two-thirds full, dispose of it as instructed by your/your child's healthcare provider. Follow any special state or local laws regarding the proper disposal of needles and syringes.
- The ENBREL® vials, vial adapters, and used alcohol swabs should be placed in the trash. The dose tray and cover may be recycled.

All questions should be answered by a healthcare provider familiar with ENBREL®. A toll-free information service is also available: 1-888-4ENBREL (1-888-436-2735).

AMGEN®

Wyeth®

Manufactured by:
Immunex Corporation,
Thousand Oaks, CA 91320-1799
Marketed by Amgen and Wyeth Pharmaceuticals

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Issued xx/2003

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This paper can be recycled.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103795 / S-5097

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike Rockville, MD 20852

Date: July 23, 2003

From: Scheldon Kress, M.D., Medical Officer
CBER/OTRR/DCTDA

To: BLA STN # 103795/5097

Through: Jeffrey Siegel, M.D.
Acting Chief, Immunology and Infectious Disease Branch
CDER/OTRR/ FDA

[redacted] Marc Walton, M.D. Acting Deputy Division Director
CDER/OTRR/ FDA

1. Attached is the review of sBLA STN # 103795/5097

BLA STN # 103795/5097

Scheldon Kress, M.D., Medical Officer
CDER/OTRR/DCTDA

Date July 23, 2003

Jeffrey Siegel, M.D.
Acting Chief, Immunology and Infectious Disease Branch
CDER/OTRR/DCTDA

7/23/03
Date

Marc Walton, M.D.
Acting Deputy Division Director
CDER/OTRR/ FDA

7/23/03
Date

Table of Contents

Appendices

I. Introduction

A. Background

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder of the joints with a female predominance. A prevalence of 1% has been reported in the adult population. The disease is characterized by a progressive inflammatory synovitis manifested by polyarticular joint swelling and tenderness. The synovitis results in erosion of articular cartilage and marginal bone with subsequent joint destruction. RA produces substantial morbidity and increased mortality. Studies of natural history of the disease indicate that within 2 years of diagnosis, patients usually experience moderate disability; after 10 years 30% are severely disabled. A complete assessment of the efficacy of any treatment for RA entails clinical, physical function, and laboratory measures.

Impairment of physical functioning may severely impact on the quality of life of patients with RA. Physical functioning is a multifaceted concept comprising a variety of outcomes. These include the ability to perform daily activities at home or in the workplace, such as personal care, eating, household maintenance, and occupational and social activities. A common feature of all these aspects of physical functioning is that they are patient self-reported, which contrasts with other outcome measures in RA such as structural damage or acute phase reactants.

Patient-reported outcomes including health-related quality of life, physical function and disability, are important outcome measures in clinical studies of patients with rheumatoid arthritis (RA). The FDA includes prevention of disability as a claim in its guidance document and requests follow-up of at least 2 years duration to support physical function labeling claims. The two instruments most commonly used to assess these patient-reported outcomes are the disability index of the Stanford Health Assessment Questionnaire (HAQ disability index) and the Medical Outcomes Study Short-Form Health Survey (SF-36). Physical functioning, as measured by the HAQ disability index and the SF-36, was a contingent primary endpoint or a secondary endpoint in clinical studies of etanercept in patients with late-stage or early RA.

The recent introduction of new classes of therapeutic agents has contributed to major advances in the treatment of RA. Three TNF-α blocking agents, infliximab, etanercept, and adalimumab have been approved for improvement in signs and symptoms of RA. In addition, the TNF-α blockers have demonstrated inhibition of progression of structural joint damage among patients with RA. More recently anakinra, the first IL-1 blocking agent, has been approved for improvement in signs and symptoms of RA. All of these agents are generally well tolerated, but have been associated with uncommon serious adverse events, primarily serious infections.

B. Regulatory History

The FDA issued a Guidance Document for evaluating new treatments of RA in February 1999 (Clinical Development Programs for Drugs, Devices, and Biological Products Intended for the Treatment of Rheumatoid Arthritis). The guidance document recognized claims for efficacy based on improvement in signs and symptoms and a group of enhanced claims. For demonstration of efficacy, the standards set forth require improvement in signs and symptoms of RA in a clinical trial of at least six months duration based on validated composite endpoints or indices of signs and symptoms such as the American College of Rheumatology (ACR) criteria for 20% improvement (the ACR20). The standard ACR criterion for improvement in RA (ACR 20) represents a reduction of at least 20% in the number of both tender and swollen joints, and an improvement of at least 20% in at least 3 of the following measures: physician's and patient's global assessments, patient's assessment of pain, patient's assessment of physical function, and measures of acute phase reactants (C-reactive protein and/or erythrocyte sedimentation rate). ACR 50 and ACR 70 results are calculated in an analogous fashion. To encourage long-term trials, the claim of improvement in physical function was defined, which requires a validated measure of improvement in disability such as the HAQ (Health Assessment Questionnaire), Arthritis Impact Measure Scale (AIMS), as well as evidence of improvement or, at least, no worsening in a measure of health related-quality of life such as the SF-36 for two to five years.

C. Etanercept Clinical Development Program

This submission summarizes the effect of etanercept (ENBREL) on physical functioning in patients with RA and proposes a label change for etanercept to add a claim for improving physical function. Data are presented from studies of etanercept-treated patients analyzing physical functioning from controlled 6 month and long-term 2 to 5 year open-label treatment of late-stage RA. In addition, the submission contains data on a controlled 1 year and long-term open-label treatment of early RA for up to 4 years. These evaluations are based on clinical trials from which clinical efficacy and safety data were used to support Immunex's Biologics License Application (BLA) and supplemental BLAs (sBLAs) for etanercept. Etanercept is currently approved for treatment of signs and symptoms of RA and for inhibition of progression of structural damage.

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

II. Overview of Physical Functioning Clinical Studies

A. Clinical Trial Design

Physical function outcomes are presented from 3 controlled trials, one open-label safety study, and 2 ongoing, open-label extension studies in patients with late-stage or early RA who have been treated with etanercept (Table 1). The etanercept clinical database utilized for this study was separated into 2 populations with distinct but sometimes overlapping characteristics:

- **Late-stage RA:**
  Patients who have previously failed one or more disease-modifying antirheumatic drugs (DMARDs). Some of these patients had ≤ 3 years of disease duration, but the average duration for the group was 10 years. Physical functioning was measured by the HAQ disability index and the data from patients with late-stage RA are presented from controlled Protocols 016.0009 (Study I) and 016.0014 (Study II); from an open-label safety study, Protocol 016.0019; and from an ongoing, open-label extension, Protocol 016.0018.

- **Early-stage RA:**
  Patients with ≤ 3 years duration of RA who were MTX-naïve; some patients had received previous DMARDs (usually hydroxychloroquine or sulfasalazine). Patients with early-stage RA are represented by data from controlled Protocol 016.0012 (Study III) and from an ongoing, open-label extension, Protocol 016.0023.

  Together, these studies provide physical functioning data for up to 5 years for late-stage and up to 4 years for early-stage RA.

Table 1 : Etanercept RA Clinical Studies -

Evaluating HAQ and SF-36 as Secondary Endpoints

Study Design		Status	Duration	No. of Patients	Physical Functioning Measures Evaluated
Patients with DMARD-failing, Late-Stage RA:					
016.0009	Placebo Etanercept 10mg twice weekly Etanercept 25 mg twice weekly	Completed	6 months	234	HAQ, SF-36 (n = 47)
016.0014	Placebo/MTX 25 mg Etanercept/MTX	Completed	6 months	89	HAQ
016.0019	Open-label 25 mg etanercept, SC twice weekly	Completed	6 months	239	HAQ
016.0018	Open-label extension of previous trials in DMARD-failing RA (25 mg etanercept SC twice weekly)	Ongoing	2 – 5 years	639*	HAQ
Patients with Early-Stage RA:					
016.0012	MTX etanercept 10 mg twice weekly etanercept 25 mg twice weekly	Completed	24 months	632	HAQ, SF-36
16.0023	Open-label extension of 016.0012 study in early, active RA (25 mg etanercept SC twice weekly)	Ongoing	2 – 5 years	468†	HAQ

DMARD = disease-modifying antirheumatic drug; HAQ = Stanford Health Assessment Questionnaire; MTX = methotrexate; SF-36 = Medical Outcomes Study Short-Form Health Survey-36

* Number of patients from Phase 1 or 2 controlled, retreatment, pediatric, and open-label studies (016.0002, 016.0004, 016.0006, 016.0008, 016.0009, 016.0014, 016.0016, 016.0019) who enrolled in open-label Protocol 016.0018.

† Number of patients from Protocol 016.0012 who enrolled in open-label Protocol 016.0023.

In study 16.0012, the primary endpoints were tested in a tiered hierarchy, structured to maintain the overall alpha level for the study at 0.05. Clinical response and prevention of radiographic progression are the 2 co-primary endpoints. Prevention of disability and health-related quality of life are the 2 first-level conditional endpoints.

The two co-primary endpoints are improvement in ACR-N response AUC over 6 months, and the mean rate of change over 12 months in the Total Sharp Score (joint erosion score plus joint space narrowing score). The two first-level conditional primary endpoints are Prevention of Disability (the HAQ disability index) and Health Related Quality of Life. First-level conditional endpoints are not tested unless at least one co-primary endpoint is met. If one or more of the co-primary endpoints are found to be statistically significant then each of the first-level conditional endpoints will be evaluated by the Hochberg method, followed by pair wise comparisons if statistical significance is met.

B. Health-Related Quality of Life – Measuring Physical Function

Health-related quality of life (HRQOL) has recently been defined by the ACR, the Outcome Measures in Rheumatoid Arthritis Clinical Trials group (OMERACT), and the FDA's guidance document as an important outcome measure of efficacy in RA clinical trials. One component of health-related quality of life is physical function.

Physical functioning is a multifaceted concept comprising a variety of outcomes. These include the ability to perform daily activities at home or in the workplace, such as personal care, eating, household maintenance, and occupational and social activities. A common feature of all these aspects of physical functioning is that they are patient self-reported. Physical function and disability were assessed in controlled and long-term studies of etanercept in patients with RA, using the HAQ disability index and the SF-36. The HAQ disability index was the primary instrument used to assess improvement in disability in both of these patient populations. SF-36 assessments were obtained from patients in the 2 year early-stage study 016.0012. However, for patients in the late-stage studies, the SF-36 assessments were added while Study 016.009 was underway and after Studies 016.0014 and 016.019 were completed. Therefore, results for late-stage RA were only available from a small subset of patients in Study 016.009.

The HAQ disability index is the most commonly used validated instrument specific to physical functioning in RA patients, it has been shown to be useful in evaluating long-term outcomes in RA. The HAQ disability index is used as one component of the ACR criteria.

The HAQ disability index is composed of 8 sub domains and 43 questions on the Immunex Case Report. Each questions relates to a patient's ability to perform tasks and activities within these 8 subdomains:

1. dressing and grooming,
2. arising,
3. eating,
4. walking,
5. hygiene,
6. reach,
7. grip
8. activity

Responses are self-rated by patients, as described below, on a 4-point Likert scale where:

1 = without any difficulty, 2 = with some difficulty,
3 = with much difficulty, 4 = unable to do.

Patients are also asked to indicate their use of aids and devices or if they need help from another person to perform any of these activities. If the patient indicates that assistance was required to achieve a score of 1 or 2, then the core is reassigned a value of 3. If the patient has completed 1 or more questions on 6 or more of the subdomains, then the disability domain of the HAQ can be computed; otherwise the HAQ score is set to missing for that visit.

The disability index is computed from the mean score of the 8 subdomains. To compute the HAQ score, the scores of the subdomains that had 1 or more completed questions are averaged. This intermediate score will range from 1–4. The final score is computed by subtracting 1 from the intermediate score. Thus, the final HAQ score is on a 0–3 scale with 0 indicating no disability and 3 indicating severe disability. The total score for the HAQ (over time as AUC) will be computed and compared between treatments. A more detailed description of the HAQ disability index is available in Appendix 1.

Health Related Quality of Life - The SF-36 Health Survey is a comprehensive short-form generic measure of health related quality of life. The survey consists of 36 items, 35 of which are aggregated into eight multi-item scales that measure:

1. ***physical functioning*** **(PF)**
2. ***role physical*** **(RP)**
3. ***bodily pain*** **(BP)**
4. *general health* (GH)
5. *vitality* (VT)
6. *social functioning* (SF)
7. *role emotional* (RE)
8. *mental health* (MH)

These eight scales are hypothesized to form two distinct higher-order clusters, physical and mental health factors, that account for more than 80-85% of the reliable variance in the eight scales in the general US population. Therefore, these two summary measures were constructed from the aggregated scores from all eight scales, and. converted into 2 summary scores: a physical component summary (PCS) and a mental component summary (MCS). Three scales **(PF, RP, and BP)** correlate most highly with the physical factor and contribute most to scoring the Physical Component (PCS). Results presented in this submission summarize the two composite scores. Raw PCS and MCS scores are then multiplied by 10 and 50 is added, so that the resulting summary scores have a mean of 50 and a standard deviation of 10. A more detailed description of the SF-36 health profile is available in Appendix II.

C. Inclusion Criteria and Study Conduct

1. Late Stage RA

Inclusion criteria for the late stage RA trials were similar and required patients to have active RA and previous failure of one or more disease-modifying antirheumatic drugs (DMARDs). Patients in this group had an average of 10 years of RA, but patients with early disease ($\leq$ 3 years duration) were not excluded if they met the other criteria (Table 2). Controlled Protocols 016.0009 and 016.0014 enrolled 323 patients and open-label safety study Protocol 016.0019 enrolled 239 patients. Patients from these and other previous trials were eligible to enter an ongoing, open-label Protocol 016.0018. All 639 patients enrolled in this study received etanercept 25 mg twice weekly.

Table 2 : DMARD-failing ("Late Stage") RA Patient Trials – at enrollment

1. Protocol 016.0009 (6-month duration - placebo-controlled)

Etanercept 25 mg twice weekly	**78**
Etanercept 10 mg twice weekly	76
Placebo	80
Total Patients	234

2. Protocol 016.0014
(6-month duration – background MTX + placebo-controlled)

Etanercept 25 mg twice weekly + MTX	59
Placebo + MTX	30
Total Patients	89

3. Protocol 016.0019 (6-month duration open-label safety study)

Etanercept 25 mg twice weekly	**239**

4. Protocol 016.0018 (ongoing open-label extension study of previous trials in DMARD-failing RA) Patients followed for 2 to 5 years.

Etanercept 25 mg twice weekly	**639**
Total Patients	639

Protocol 016.0009 was a double-blind, placebo-controlled, multicenter Phase 3 study in which patients with active RA were randomized to receive either placebo or 10 or 25 mg etanercept administered SC twice weekly for 6 months. Patients could receive stable concomitant doses of corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs). All patients were allowed to continue receiving treatment in a blinded fashion until disease exacerbation or until the database for the 6-month evaluation of all patients was locked at Immunex Corporation.

Protocol 016.0014 was a double-blind, placebo-controlled, multicenter Phase 3 study in which patients with active RA who had been receiving background methotrexate (MTX) for at least 6 months were randomized to receive 25 mg of etanercept or placebo by twice-weekly SC injection, added to their MTX. All patients were to have been on oral or SC MTX for 6 months with a stable dose of 15 to 25 mg/week for at least 4 weeks. Patients could receive stable concomitant doses of corticosteroids or NSAIDs. Patients were allowed to continue receiving treatment with blinded study drug until the database for the 6-month evaluation for all patients was locked at Immunex Corporation.

Protocol 016.0019 was an open-label multicenter study in which patients with active RA were to receive 25 mg etanercept administered SC twice weekly for 6 months. Patients could receive stable concomitant doses of corticosteroids or NSAIDs.

Protocol 016.0018 is an ongoing, long-term extension study in which patients from Protocols 016.0009, 016.0014, and 016.0019 (and other studies of patients with late-stage RA) receive open-label 25 mg etanercept administered SC twice weekly.

2. Early Stage RA

Inclusion criteria for the early stage RA trials required patients to have active RA with ≤ 3 years duration and to be methotrexate (MTX)-naïve (Table 3) Patients may have previously failed another DMARD (usually hydroxychloroquine or sulfasalazine). Radiographic results were also assessed in this patient population.

Table 3 : Early Stage RA Patient Trials – at enrollment

1. Protocol 016.0012 (24 month duration - active-controlled - one year blinded)

Etanercept 25 mg twice weekly	**207**
Etanercept 10 mg twice weekly	208
MTX	217
Total Patients	632

2. Protocol 016.0023 (open-label extension study of previous trial)

Etanercept 25 mg twice weekly	**467**
Total Patients	467

Protocol 016.0012 was a double-blind, active-controlled, double-dummy, multicenter, Phase 3 trial in which adult patients with active, early (diagnosed ≤ 3 years) RA who had not previously received MTX were randomized to receive 10 mg or 25 mg etanercept (SC twice weekly) or rapidly dose-escalated oral MTX (median of 20 mg/week after the dose escalation period) for at least 12 months. After all patients had received blinded treatment with MTX or etanercept in the initial treatment period, patients who remained in the trial continued to receive open-label treatment with the originally assigned medication until completion of the second year.

Protocol 016.0023 is an ongoing, long-term extension study in which patients from Protocol 016.0012 receive open-label 25 mg etanercept administered SC twice weekly.

Table 4 summarizes the original source study for patients rolled over into the two long-term studies 016.0018 (late-stage) and 016.0023 (early-stage) and the number of patients enrolled and remaining at each 3 month interval in each study during the initial 2 year period of observation.

Table 4: Patients Entering Two Year Studies (Based on Original Grouping)

Study		Patients Enrolled and Remaining in Study at Month								
		0	3	6	9	12	15	18	21	24
Patients with DMARD-failing, late-stage RA Rolled Over Into Study 016.0018										
016.0009	Placebo	71	67	67	67	66	65	63	62	62
	Etanercept 10mg twice weekly	76	67	66	63	59	56	52	51	50
	Etanercept 25 mg twice weekly	**78**	**62**	**61**	59	59	56	54	54	52
016.0014	Placebo/MTX	26	25	23	23	23	22	21	20	20
	25 mg Etanercept/MTX	59	57	54	52	51	50	49	49	48
016.0019	Open-label 25 mg etanercept, SC twice weekly	**239**	**219**	**206**	201	195	187	182	181	177
Patients with early-stage RA Rolled Over Into Study 016.0023										
016.0012	MTX (rapid-escalation)	217								143
	Etanercept 10 mg twice weekly	208	194	187	180	177	172	169	169	163
	Etanercept 25 mg twice weekly	**207**	**193**	**190**	**181**	**178**	173	170	168	162
016.0023	Etanercept 25 mg (MTX group) [1]	143	134	131	127	127	124 [2]		122 [3]	104
	Etanercept 25 mg (10 mg group) [1]	163	156	153	149	144	142 [2]		141 [3]	111
	Etanercept 25 mg (25 mg group) [1]	162	156	153	150	144	139 [2]		134 [3]	106

[1] Patients in this group originally received different treatments in Study 016.0012, but in this Study they all received Etanercept 25 mg twice weekly.
[2] Month 16
[3] Month 20
Boxed areas randomized, double-blinded, and controlled

D. Efficacy Analyses

1. Definition of Improvement

Sustained improvement, defined as improvement of > 0.25, > 0.50, and >1.00 units in the HAQ score through 2 years relative to baseline, is further defined as follows for patients treated with 25 mg etanercept. The definitions of sustained improvement are different for etanercept- and placebo-treated patients in that etanercept-treated patients had to meet the specified level of improvement at 6 months and time-points out to 2 years, while placebo-treated patients were counted as meeting the end-point if they were improved at 6 months. Thus the criteria were more stringent for etanercept-treated patients.

Sustained improvement (Observed)

Defined as patients :

- Treated with 25 mg etanercept:
- Improvement of: >0.25, >0.50, and >1.00 units in the HAQ score
- Sustained improvement for 2 years relative to baseline,
- Improvement observed at both 6 months and 24 months (or 28 months if no visit occurred in the 24-month window) and was improved or missing at all visits between 6 months and 24 months.

The number of patients with sustained improvement as defined above was then divided by the total number of patients treated with 25 mg etanercept in the controlled trial (n = 78 for Protocol 016.0009 and n = 59 for Protocol 016.0014) to obtain the sustained rate of improvement for 2 years.

Sustained improvement (LOCF):

Defined as patients :

- Treated with 25 mg etanercept:
- Improvement of: >0.25, > 0.50, and >1.00 units in the HAQ score
- Sustained improvement (LOCF) for 2 years relative to baseline,
- Improvement was observed at 6 months and at least one time point beyond 6 months up to 24 months, and was improved or missing at all points beyond 6 months up through 24 months.

Thus, if a patient had missed a visit or had discontinued prior to Month 28, but achieved improvement at all observed time points, then the patient had sustained improvement (LOCF). The number of patients with sustained improvement (LOCF) as defined above was then divided by the total number of patients treated with 25 mg etanercept in the controlled trial (n = 78 for Protocol 016.0009 and n = 59 for Protocol 016.0014) to obtain the sustained (LOCF) rate of improvement for 2 years.

Qualified LOCF:
If missing value was due to discontinuation for lack of efficacy, the value was counted as "No" (indicating HAQ did not reach zero or did not improve).

Sustained improvements as defined above for patients who received 25 mg etanercept were compared to corresponding rates for **placebo patients**, which are further defined as follows:

Sustained improvement (Observed)

A patient in the placebo group in either controlled trial was classified as having sustained improvement if the patient was observed to have improved at 6 months in the controlled trial. The number of placebo patients observed to have improved at 6 months was then divided by the total number of placebo patients in the controlled trial (n = 80 for Protocol 016.0009 and n = 30 for Protocol 016.0014) to obtain the sustained rate of improvement for 2 years for the placebo patients.

Sustained improvement (LOCF)

A patient in the placebo group in each controlled trial was classified as having sustained (LOCF) improvement if the patient was observed to have improved at 6 months OR at the last recorded assessment prior to 6 months. The number of placebo patients with sustained improvement (LOCF) as defined above was then divided by the total number of placebo patients in the controlled trial (n = 80 for Protocol 016.0009 and n = 30 for Protocol 016.0014) to obtain the sustained (LOCF) rate of improvement for 2 years for the placebo patients

Comparisons of sustained improvement were done using Fisher's Exact test. For each of Protocols 016.0009 and 016.0014 and the relevant long-term experience in Protocol 016.0018, statistical comparisons for improvement and percent improvement in HAQ were done using one-way analysis of variance with pair wise comparison assessed using standard error from ANOVA model. Proportions derived from the HAQ score were compared using likelihood-ratio chi-square tests.

2. Data Instability

Frequently, in this submission the actual numbers of patients appearing in the various tables for the same timepoint do not match. Combinations of factors contributed to these discrepancies at specific timepoints, such as 1.) the inability to discern if a patient had withdrawn from the trial or had just missed a planned visit, or 2.) Inability to discern if a patient had discontinued prior or continued into a longer-term study. Although similar windows were used to define the time points, efficacy data was occasionally collected at later follow-up visits and those later data were used in later analyses. Overall, these discrepancies represented only a few patients and therefore did not have an impact on the overall observed efficacy. Examples of these discrepancies can be found in Appendix 2.

3. Analysis of the Data

Available HAQ and SF-36 results from adult patients enrolled in these Protocols are summarized using all data available up to the data cut-off for this submission (April 2, 2002 for Protocol 016.0018; other studies are closed). Results are described as statistically significant when p-values are < 0.05 (2-sided). Confidence intervals are 95% (2-sided), based on raw estimates for standard deviation. No adjustments for multiplicity were made.

For each of the controlled studies 016.0009 and 016.0014, the HAQ disability index is presented over time during the 6-month blinded phase as raw score, change, and percent change in score from baseline for each treatment group. In addition, the following proportions of patients are presented over time:

- Proportion with HAQ = 0 (no disability)
- Proportions with HAQ improvement from baseline ≥ 0.25, ≥ 0.50, and ≥ 1.00 units (0.22 units is considered clinically important)

III. ACR 20, ACR 50, ACR 70 Responses

This evaluation is based on clinical trials from which clinical efficacy and safety data were used to support Immunex's Biologics License Application (BLA) and supplemental BLAs (sBLAs) for etanercept 25 mg twice weekly. Studies 16.0009 and 16.0014 in late-stage RA both met their primary endpoint of ACR20 with etanercept 25 mg sc biweekly compared to placebo. Study 16.0012 in early-stage RA met its primary endpoint of ACR-n AUC in comparison to MTX.

Table 5 shows the ACR 20, 50, and 70 responses of patients in long-term, open label studies for the late-stage patients. Table 6 shows the ACR 20, 50, and 70 responses at the end of the controlled portion of Study 16.0012 and at the initiation of, and 12 –month time point in the open-label extension study in the early-stage patients. The proportion of patients attaining and maintaining ACR 20, 50, and 70 responses in response to etanercept-treatment are similar in the two patient populations.

Table 5 : Percent ACR Responders in Patients with Late-stage RA*
in Long-Term, Open-Label Extension Studies

ACR Response	12 months (n = 560)	24 months (n = 412)	36 months (n = 342)	48 months (n = 98)
ACR 20	70%	72%	73%	74%
ACR 50	44%	44%	47%	49%
ACR 70	19%	21%	26%	26%

* Protocols 016.0008, 016.0009, 016.0014, 016.0018, 016.0019.

Table 6 : Percent ACR Responders in Patients with Early-stage RA*
In Controlled and Long-Term, Open-Label Extension Studies

	25 mg Etanercept			
	Controlled Study		Open-label Study	
	12 months	24 months	Baseline	12 months
ACR Response	(n = 177)	(n = 152)	(n = 160)	(n = 119)
ACR 20	75%	84%	82%	76%
ACR 50	53%	59%	56%	55%
ACR 70	27%	36%	34%	34%

* Protocols 016.0012 and 016.0023.

IV. Late-Stage RA Long-Term Trials

A. Analysis of the Outcome

The HAQ scores were collected over time in Protocol 016.0018, the long-term trial of patients with late-stage RA. The raw scores, percent change, and proportions described above for the controlled trials are presented over time in the long-term trial for the following subsets:

- Patients who received 25 mg etanercept in Protocol 016.0009.
- Patients who received 25 mg etanercept + MTX or placebo + MTX in Protocol 016.0014
- Pooled analysis: all patients from Protocols 016.0009 and 016.0019 (note that experience was measured relative to last value prior to receiving etanercept in Protocol 016.0018 for placebo patients in Protocol 016.0009 who started etanercept in 016.0018).
- Additional notes:
  This cohort includes experience from patients originally on 10 mg in Protocol 016.0009 and on MTX (concomitant or monotherapy) in Protocol 016.0014 [patients in both of these groups were excluded from the pivotal physical function analysis].

The cohorts described above and their inclusion in or exclusion from the late-stage long-term Supportive Data are shown in Table 7.

Table 7 : Late-Stage RA Patients Treated with Etanercept Twice Weekly – Evaluated for Physical Function

Studies (Late-Stage RA)		Number Originally Enrolled - Some Excluded *	Number Actually Enrolled	Number Actually Completed Study 2 Years	Number Included Long-Term Tables *
016.0009 [1] 6 Month	Placebo	80	71	47	**69**
	10 mg Etanercept	76	66 [4]	42	**73**
	25 mg Etanercept	**78**	**61**	**43**	**75**
016.0014 [2] 6 Month	Placebo/MTX	30	26	0	22
	25 mg Etanercept/MTX	59	53	45	57
016.0019 [3] 6 Month	**25 mg Etanercept Open-label**	**239**	**209**	**146**	**233**
016.0018 25 mg Etanercept [4] Duration 2 - 5 Years		639 [5]		Total 323	Total 450 [6]

* Patients who discontinued prior to the 3-month window (Day 46 visit) are excluded from the long-term tables and analysis.

[1] Allowed concomitant low-dose corticosteroid and/or NSAID

[2] Background MTX - stable dose ≥ 6 months. Patients on MTX were excluded from long-term analysis.

[3] Allowed concomitant stable low-dose corticosteroid or NSAID

[4] Patients who received 10 mg Etanercept in 016.0009 had the option to continue on 10 mg Etanercept or increase the dose to 25 mg Etanercept in 016.0018

[5] Patients came from many additional phase I and II protocols also.

[6] Late-Stage RA Patients in Pooled Tables (includes bolded numbers from long-term column above, excluding patients on MTX)

Only patients who had a post-baseline visit after Day 46 visit were included in long-term tables of results. For example, in Protocol 016.0009, 3 of the 78 patients in the 25 mg etanercept group left the study prior to Day 46; thus, only 75 patients in that group appear in long-term tables for this study. In Protocol 016.0014, 2 of the 59 patients in the etanercept/MTX group left the study prior to Day 46; thus, only 57 of the patients in that group appear in the long-term tables for this study.

B. Health Assessment Questionnaire Results

Patient responses on the HAQ disability index are submitted as primary data in the physical functioning claim for etanercept. Data are available from patients with late-stage RA who were treated in Protocols 016.0009, 016.0014, 016.0018, and 016.0019, and from patients with early RA who were treated with etanercept or MTX in Protocols 016.0012 and 016.0023.

1. HAQ Results At Years One and Two

Protocol 016.0009 – Etanercept as Monotherapy

Two hundred thirty-four patients were treated with blinded monotherapy, 78 patients in the etanercept 25 mg group, 76 patients in the etanercept 10 mg group, and 80 patients in the placebo group. Table 8 summarizes the results for the HAQ disability index over time in the 6-month controlled study, using the LOCF analysis.

Table 8 : Protocol 016.0009: HAQ Disability Index (LOCF) – 6 Month Study

		Etanercept		P-values*	
	Placebo (n = 80)	10 mg (n = 76)	25 mg (n = 78)	Placebo vs 10 mg	Placebo vs 25 mg
Mean value†					
Baseline	1.7	1.7	1.6		
Week 2	1.7	1.4	1.3		
Month 1	1.6	1.4	1.2		
Month 3	1.6	1.3	1.1		
Month 6	1.7	1.2	1.0		
Mean improvement from baseline					
Week 2	0.07	0.29	0.30	0.0001	< 0.0001
Month 1	0.09	0.36	0.44	< 0.0001	< 0.0001
Month 3	0.12	0.47	0.54	< 0.0001	< 0.0001
Month 6	0.03	0.52	0.57	< 0.0001	< 0.0001
(Month 6 – 95% C.I.)	(-0.06, 0.12)	(0.41, 0.63)	(0.43, 0.71)		
Mean % improvement from baseline					
Week 2	4%	16%	17%	0.0050	0.0012
Month 1	6%	23%	31%	0.0007	< 0.0001
Month 3	8%	30%	36%	0.0002	< 0.0001
Month 6	2%	34%	39%	< 0.0001	< 0.0001
(Month 6 – 95% C.I.)	(-5%, 8%)	(26%, 42%)	(31%, 48%)		

* P-value determined by one-way ANOVA with pairwise comparisons assessed using standard error from ANOVA model.

† Range: 0 = best assessment, 3 = worst assessment.

The HAQ disability index was significantly improved from baseline throughout the study in patients treated with either 10 mg or 25 mg etanercept, compared to patients treated with placebo. Improvement was observed as early as 2 weeks after initiation of study drug. Reports in the literature have established a difference of 0.22 units in the HAQ disability index as clinically important.[1] At 6 months, patients in the 10 mg etanercept group had improved by a mean of 0.52 units, and patients in the 25 mg etanercept group by 0.57 units. In both etanercept-treated groups, the mean improvement exceeded the minimal clinically important difference. Of note, no improvement was observed in the placebo group.

Additional analyses of the HAQ disability index in Protocol 016.0009 included the number of patients who achieved improvements > 0.25, > 0.5, or > 1.0 units in the HAQ scores as well as those patients who achieved a HAQ score of 'zero'. Table 9 summarizes the results of these additional analyses at 6 months in the placebo controlled study, using the qualified LOCF analysis (where a missing value was counted as "did not achieve response" if it was due to patient's discontinuation for lack of efficacy or by LOCF otherwise).

Table 9 : Protocol 016.0009 Late-Stage: Additional HAQ Assessments at 6 Months (Qualified LOCF Analysis – missing values Imputed as LOCF or No Response If Due to Lack of Efficacy)

		Etanercept		P-values*	
	Placebo (n = 80)	10 mg (n = 76)	25 mg (n = 78)	Placebo vs 10 mg	Placebo vs 25 mg
Patients with zero HAQ score	0%	7%	15%	0.0066	< 0.0001
Patients with decrease of ≥ 0.25 in HAQ	23%	67%	65%	< 0.0001	< 0.0001
Patients with decrease of ≥ 0.5 in HAQ	13%	47%	50%	< 0.0001	< 0.0001
Patients with decrease of ≥ 1.0 in HAQ	3%	20%	20%	0.0003	0.0002

* P-value determined by likelihood ratio chi-square test.

In Protocol 016.0009, significantly more patients treated with 10 mg or 25 mg etanercept achieved these benchmarks of improvement in the HAQ scores, compared to patients in the placebo group.

[1] Wells GA, Tugwell P, Gunnar RK, Baker PRA, Groh J, Redelmeier DA: Minimum important difference between patients with rheumatoid arthritis: the patients perspective. *J Rheumatology* 1993;20:557-60

Protocol 016.0014 – Etanercept Added to Background Methotrexate

Eighty-nine patients with active RA despite at least 6 months of MTX therapy were enrolled, randomized, and received blinded study drug in addition to background MTX, 59 patients in the etanercept/MTX group and 30 patients in the placebo/MTX group.

Table 10 summarizes the results for the HAQ disability index over time in the 6-month controlled study, using the LOCF analysis.

Table 10 : Protocol 016.0014 Late-Stage: HAQ Disability Index (LOCF Analysis)

	Placebo/MTX (n = 30)	Etanercept/MTX (n = 59)	P-values*
Mean value†			
Baseline	1.3	1.5	
Week 1	1.3	1.2	
Month 1	1.2	1.1	
Month 3	1.2	0.9	
Month 6	1.2	0.9	
Mean improvement from baseline			
Week 1	0.09	0.25	0.0272
Month 1	0.16	0.39	0.0033
Month 3	0.17	0.53	0.0006
Month 6	0.18	0.58	0.0002
(Month 6 – 95% C.I.)	(0.05, 0.31)	(0.45, 0.71)	
Mean % improvement from baseline‡			
Week 1	4%	16%	0.0651
Month 1	10%	30%	0.0040
Month 3	14%	37%	0.0012
Month 6	12%	44%	0.0002
(Month 6 – 95% C.I.)	(-0.3%, 24%)	(34%, 54%)	

* P-value determined by one-way ANOVA (t-test).
† Range: 0 = best assessment, 3 = worst assessment.
‡ Due to zero baseline values, one patient was omitted from each treatment group.

The HAQ disability index was significantly improved from baseline at 1, 3, and 6 months in patients treated with etanercept/MTX compared to patients treated with placebo/MTX. Improvement was observed as early as one week after patients received the first dose of etanercept. The mean improvement in HAQ for patients in the etanercept group exceeded the threshold for clinically important improvement (0.22 units), but not for patients in the placebo group. Analyses of the HAQ disability index in Protocol 016.0014 for the number of patients who achieved improvements $\geq$ 0.25, $\geq$ 0.5, or $\geq$ 1.0 units in the HAQ scores as well as those patients who achieved a 'zero' HAQ score at month 6 are summarized in Table 11 using the qualified LOCF analysis.

Table 11 : Protocol 016.0014: Additional HAQ Assessments at 6 Months (Qualified LOCF Analysis)

	Placebo/MTX (n = 30)	Etanercept/MTX (n = 59)	P-values*
Patients with zero HAQ score	3%	15%	0.0657
Patients with decrease of ≥ 0.25 in HAQ	37%	75%	0.0005
Patients with decrease of ≥ 0.5 in HAQ	20%	58%	0.0005
Patients with decrease of ≥ 1.0 in HAQ	7%	24%	0.0340

* P-value determined by likelihood ratio chi-square test.

In Protocol 016.0014, significantly more patients treated with etanercept/MTX achieved these levels of improvement in the HAQ scores, compared to patients who received MTX alone.

2. Long-term HAQ Results Through Five Years

Protocols 016.0009 to 016.0018 – Etanercept as Monotherapy

Patients treated with blinded study drug in Protocol 016.0009 could enroll in Protocol 016.0018 and receive open-label etanercept. All patients who had originally received placebo in the blinded study began receiving etanercept at a dose of 25 mg twice weekly in Protocol 016.0018. However, patients who received 10 mg etanercept in the original study could either continue at that dose in Protocol 016.0018 or they could choose to increase their dose to 25 mg etanercept. Of note, all patients were permitted to decrease or discontinue their use of corticosteroids in the open-label study.

Table 12 summarizes the LOCF (for continuous variables) and qualified LOCF (for binary variables) results over time for the HAQ disability index for those patients who received open-label etanercept monotherapy at a dose of 25 mg SC twice weekly in Protocols 016.0009 and 016.0018.

Table 12 : Protocols 016.0009 to 016.0018 (Etanercept 25 mg Patients Only): Mean LOCF and Qualified LOCF HAQ Results From Baseline through Data Cut-off

	Controlled		Open-label				
	Baseline (n = 78)	6 mo. (n = 78)	12 mo. (n = 75)*	24 mo. (n = 75)*	36 mo. (n = 75)*	48 mo. (n = 75)*	60 mo. (n = 75)*
Mean HAQ score†	1.6	1.0	1.0	1.0	0.9	1.0	1.0
Mean improvement from baseline in HAQ score	---	0.57	0.60	0.64	0.68	0.64	0.61
Mean % improvement from baseline in HAQ score	---	39%	40%	39%	41%	40%	38%
Patients with zero HAQ score	0%	15%	15%	13%	16%	16%	17%
Patients with decrease of ≥ 0.25 in HAQ	---	65%	65%	68%	67%	67%	68%
Patients with decrease of ≥ 0.5 in HAQ	---	50%	51%	57%	56%	59%	53%
Patients with decrease of ≥ 1.0 in HAQ	---	21%	25%	31%	39%	32%	28%

* Three patients in Protocol 016.0009 who left the study prior to the 3-month window are excluded from long-term results

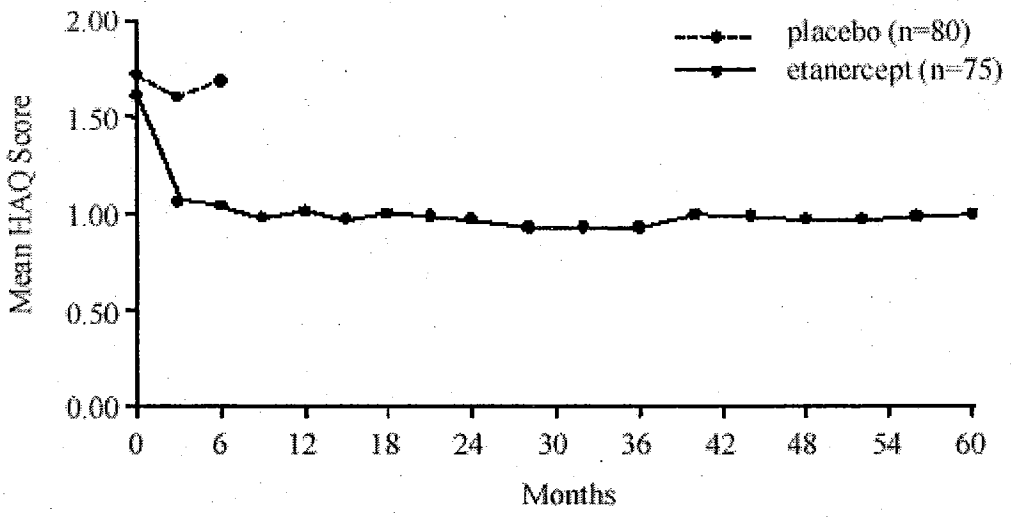
† Range: 0 = best assessment; 3 = worst assessment.

Improvement in HAQ scores both observed and LOCF with continued etanercept monotherapy from baseline through 60 months for patients with late-stage RA is shown in Table 13. The mean HAQ improvement from baseline seen at the end of the controlled study, was sustained for patients treated with etanercept in the extension study. Mean HAQ scores improved from a baseline of1.61 units to 0.88 (observed) and 1.00 (LOCF) units at 60 months. Improvement in mean HAQ ≥ 0.25 occurred in over 80% (observed) and approximately 70% (LOCF), mean HAQ ≥ 0.50 occurred in approximately 70% (observed) and over 50% (LOCF), mean HAQ ≥ 1.00 occurred in approximately 30% (observed and LOCF) throughout the five year observation period. Approximately 20% of patients treated with etanercept 25 mg twice weekly attained mean HAQ scores of "0" from month 6 through month 60.

Table 13 : Comparison of Observed and LOCF HAQ Results Among Patients with Late-Stage RA Treated With Etanercept 25 mg Twice Weekly and Rolled Over From Study 016.0009 Into 016.0018

	Controlled		Open Label													
			Months													
	Baseline	6	9	12	15	18	21	24	28	32	36	44	48	52	56	60
Observed n =	75	63	63	59	57	56	49	37	50	49	45	44	40	40	37	29
HAQ mean	1.61	0.92	0.88	0.91	0.82	0.88	0.85	0.85	0.73	0.71	0.73	0.80	0.72	0.77	0.80	0.88
HAQ = 0 %	0	17	17	19	18	21	16	22	26	27	22	18	25	28	19	28
Improvement																
HAQ ≥ 0.25 %		79	81	80	81	79	82	84	86	84	84	86	88	88	92	90
HAQ ≥ 0.50 %		60	62	63	70	61	72	70	72	71	71	73	83	78	84	72
HAQ ≥ 1.0 %		25	32	31	33	36	39	41	42	53	47	34	40	38	43	34
LOCF n =	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
HAQ mean	1.61	1.00	0.98	1.01	0.97	1.01	0.99	0.97	0.93	0.93	0.93	0.99	0.97	0.97	0.99	1.00
HAQ = 0 %	0	17	16	15	13	16	12	13	19	19	16	13	16	19	16	17
Improvement																
HAQ ≥ 0.25 %		71	72	68	69	68	69	71	71	68	69	69	69	71	69	71
HAQ ≥ 0.50 %		55	55	52	57	53	59	59	57	56	57	55	60	59	57	55
HAQ ≥ 1.0 %		24	28	25	28	31	31	31	35	40	39	28	32	29	29	28

Improvement in HAQ scores at 6 months was sustained through 5 years with continued etanercept monotherapy, as shown in Figure 1. The mean improvement from baseline of 0.6 units, seen at the end of the controlled study, was sustained for patients treated with etanercept in the extension study.



Note: Standard errors for HAQ score over time for the etanercept group are consistently 0.09

Figure 1 : Protocols 016.0009 to 016.0018: Mean LOCF HAQ Scores Over Time

C. Sensitivity Analyses

An additional set of analyses was performed to assess sustained improvement in each individual patient, In these analyses, a patient treated with etanercept was considered to have achieved "sustained improvement" of 0.25, 0.5, and 1.0 units of the HAQ for 2 years only if the patient met ALL of the following conditions:

- Receiving etanercept at the 6-month time point.
- Achieved the described level of improvement (0.25, 0.5, 1.0 HAQ units) at the 6-month time point.
- Achieved the described level of improvement at 24 months (or 28 months if there was no evaluation in the 24-month time interval) and was improved or missing at all visits between 6 months and 24 months.

These analyses were performed in 2 ways: sustained (the most stringent analysis for the etanercept group), which required patients to be receiving etanercept at 24- or 28-month visit; and sustained (LOCF), which allowed LOCF of last available visit. For comparison, the placebo patients were considered to have achieved "sustained improvement" in these parameters if the patient achieved the described level of improvement at 6 months (sustained) or at the last evaluation if the patient discontinued prior to 6 months (sustained [LOCF]) as shown in Table 14.

Table 14 : Classification of Patients for Sensitivity Analysis

Enbrel Group

Sustained – Improvement at 6 and 24 months
All interim evaluations improved or missing

Sustained (LOCF) – Last evaluation as responder between 6 and 24 months
At least one evaluation after month 6

Placebo Group

Sustained – Improvement at 6 months

Sustained (LOCF) – Improvement at last evaluation if discontinued prior to 6 months

Thus, all placebo patients were conservatively credited with a "sustained response" even though they may have achieved a response at only a single visit. Conversely, patients without an improvement pattern at 6 months, even with improvement at later time points are counted as failures in this analysis. Results are summarized in Table 15.

Table 15 : Protocols 016.0009 to 016.0018 (Etanercept 25 mg vs. Placebo): Sustained HAQ Results From Baseline through Data Cut-off

	Sustained Rates			Sustained (LOCF) Rates		
	Placebo	Etanercept 25 mg	P-value*	Placebo	Etanercept 25 mg	P-value*
Patients with decrease of ≥ 0.25 in HAQ (n[%])	15/80 (19%)	34/78 (44%)	0.001	23/80 (29%)	39/78 (50%)	0.009
Patients with decrease of ≥ 0.50 in HAQ (n[%])	8/80 (10%)	24/78 (31%)	0.001	12/80 (15%)	26/78 (33%)	0.009
Patients with decrease of ≥ 1.0 in HAQ (n[%])	1/80 (1%)	8/78 (10%)	0.017	2/80 (3%)	10/78 (13%)	0.017

* P-value determined by Fisher's exact test.

Using these stringent criteria, a significantly higher proportion of the 25 mg etanercept group achieved "sustained improvement" in HAQ scores for 2 years compared with the imputed rate for the placebo group.

Protocol 016.0014 to 016.0018 –
Etanercept Added to Background Methotrexate

Of the 89 patients treated with blinded study drug in Protocol 016.0014, 79 patients (53 in the original etanercept/MTX group and 26 in the original placebo/MTX group) enrolled in Protocol 016.0018 and received 25 mg open-label etanercept in addition to background MTX. During the open-label extension trial, patients were permitted to decrease or discontinue their use of corticosteroids or MTX. As previously reported to FDA in the 3-year safety information submitted to License Number 1132 on December 20, 2001 (STN BL 103795/5051), 60% of patients either decreased their dose of MTX or discontinued it, while maintaining their clinical response, during the first year of the extension study. This trend was continued during the second and third years (62% and 57%, respectively). Calculation of these proportions of patients able to reduce dosage or discontinue MTX does not take into account the lack of a comparison control group, reductions in response to toxicity, or patient withdrawals from the studies. However, even when patient withdrawals were taken into account, substantial proportions of patients were able to reduce corticosteroids or MTX to 50% or less of their baseline dose or to discontinue entirely.

Table 16 summarizes the LOCF (for continuous variables) and qualified LOCF (for binary variables) results for the HAQ disability index for those patients who received etanercept/MTX in Protocols 016.0014 and 016.0018.

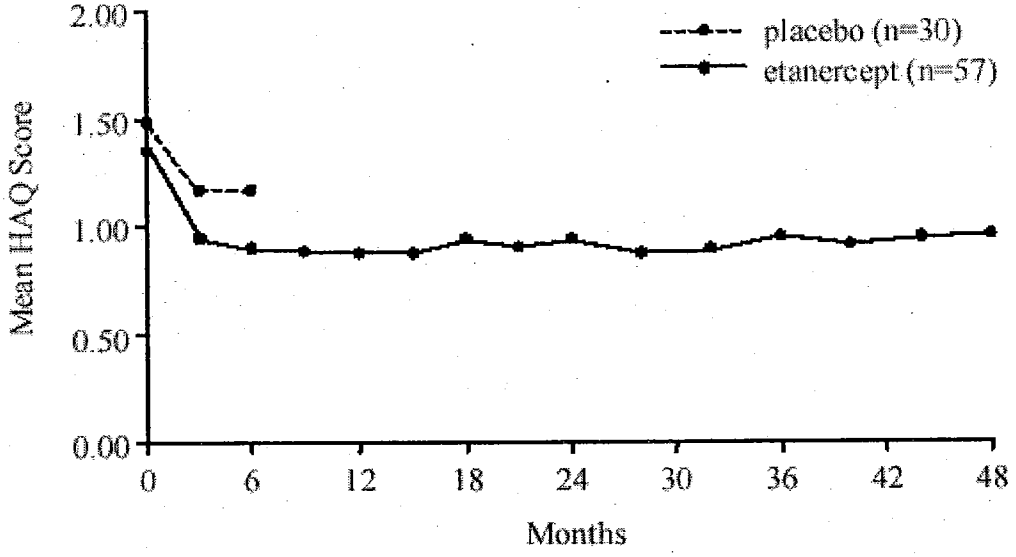
Table 16 : Protocols 016.0014 to 016.0018 (Etanercept/MTX Patients Only): Mean LOCF and Qualified LOCF HAQ Results From Baseline through Data Cut-off

	Controlled		Open-label			
	Baseline (n = 59)	6 mo. (n = 59)	12 mo. (n = 57)*	24 mo. (n = 57)*	36 mo. (n = 57)*	48 mo. (n = 57)*
Mean HAQ score†	1.5	0.9	0.9	0.9	1.0	1.0
Mean improvement from baseline in HAQ score	---	0.57	0.59	0.52	0.51	0.50
Mean % improvement from baseline in HAQ score	---	44%	43%	38%	40%	38%
Patients with zero HAQ score	2%	15%	12%	14%	16%	12%
Patients with decrease of ≥ 0.25 in HAQ	---	75%	74%	65%	68%	68%
Patients with decrease of ≥ 0.5 in HAQ	---	58%	58%	53%	56%	54%
Patients with decrease of ≥ 1.0 in HAQ	---	24%	23%	23%	21%	18%

* Two patients in Protocol 016.0014 who left the study prior to the 3-month window are excluded from long-term results

† Range: 0 = best assessment; 3 = worst assessment.

Improvement in HAQ scores was sustained with continued etanercept therapy, as shown in Figure 2.



Note: Standard errors for HAQ score over time for the etanercept group are consistently 0.09

Figure 2 : Protocols 016.0014 to 016.0018: Mean LOCF HAQ Scores Over Time

Sensitivity Analysis

As with Protocol 016.0009, an additional set of analyses was performed in Protocol 016.0014 to assess "sustained improvement" in each individual patient, i.e. improvement patterns for patients on 25 mg etanercept with responses observed at 6 months through data cut-off. Results are summarized in Table 17.

Table 17 : Protocols 016.0014 to 016.0018:

Sustained HAQ Results From Baseline through Data Cut-off

	Sustained Rates			Sustained (LOCF) Rates		
	Placebo/ MTX	Etanercept/ MTX	P-value*	Placebo/ MTX	Etanercept/ MTX	P-value*
Patients with decrease of ≥ 0.25 in HAQ (n[%])	10/30 (33%)	29/59 (49%)	0.181	11/30 (37%)	30/59 (51%)	0.262
Patients with decrease of ≥ 0.50 in HAQ (n[%])	6/30 (20%)	19/59 (32%)	0.319	6/30 (20%)	20/59 (34%)	0.221
Patients with decrease of ≥ 1.0 in HAQ (n[%])	2/30 (7%)	5/59 (8%)	1.000	2/30 (7%)	5/59 (8%)	1.000

* P-value determined by Fisher's exact test.

Using these stringent criteria, higher numbers of patients in the 25 mg etanercept/MTX group achieved "sustained improvements" in HAQ scores through 2 years compared with the placebo/MTX group. Although the differences in rates compared to control did not reach statistical significance, the proportions of etanercept-treated patients achieving sustained improvement in HAQ were similar to those seen with the 25 mg etanercept group in Protocol 016.0009.

D. Late-stage RA Studies - Pooled

A pooled analysis was performed of all late-stage RA patients who received placebo or etanercept monotherapy in Protocol 016.0009 and Protocol 016.0019 (a 6-month open-label safety study), and who subsequently entered the long-term, open-label extension study, Protocol 016.0018. Of interest, during the open-label extension trial, patients were permitted to decrease or discontinue corticosteroid use. Results of analyses of corticosteroid withdrawal were previously reported to FDA in the 3-year safety information submitted to License Number 1132 on December 20, 2001 (Reference Number STN BL 103795/5051). In the late-stage RA population identified in that submission (which included studies that did not collect HAQ data), 57% of patients either decreased their dose of corticosteroids or discontinued them, while maintaining their clinical response, during the first year of the long-term extension study. Additional patients decreased or discontinued corticosteroids during the second and third years (66% and 72%, respectively).

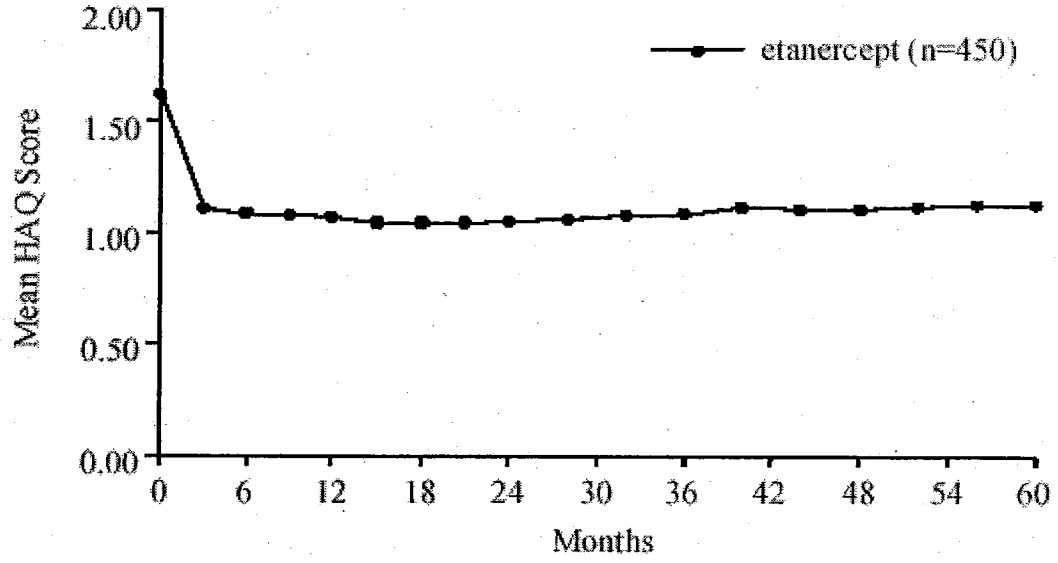
Table 18 summarizes the HAQ results for patients in Protocols 016.0009 and 016.0019 from the initial start date of etanercept therapy over time in the open-label extension study, using LOCF analyses for continuous variables and qualified LOCF analyses for binary variables.

Table 18 : Late-stage RA Studies Pooled: Mean LOCF and Qualified LOCF HAQ Results From Baseline through Data Cut-off

	Baseline (n = 450)	12 months (n = 450)	24 months (n = 450)	36 months (n = 450)	48 months (n = 450)	60 months (n = 450)
Mean HAQ score*	1.6	1.1	1.1	1.1	1.1	1.1
Mean improvement from baseline in HAQ score	---	0.56	0.57	0.54	0.51	0.50
Mean % improvement from baseline in HAQ	---	35%	36%	32%	31%	30%
Patients with zero HAQ score	< 1%	12%	11%	11%	12%	12%
Patients with decrease of ≥ 0.25 in HAQ	---	72%	68%	66%	64%	64%
Patients with decrease of ≥ 0.5 in HAQ	---	51%	53%	49%	49%	47%
Patients with decrease of ≥ 1.0 in HAQ	---	24%	24%	25%	22%	21%

* Range: 0 = best assessment; 3 = worst assessment.

In this larger sample of patients with late-stage RA, improvement in HAQ scores was sustained with continued etanercept therapy and supports the results from the cohorts previously described in the controlled studies. Mean HAQ scores over time, using the LOCF analysis, are shown in Figure 3.



Note: Standard errors for HAQ score over time for the etanercept group are consistently 0.04

Figure 3 : Late-Stage RA Studies Pooled: Mean LOCF HAQ Scores Over Time

V. Early-Stage RA Long-Term Trials

A. Analysis of the Data

The physical function assessments (HAQ and SF-36) of patients enrolled in Protocols 016.0012 and 016.0023 were summarized using all data available up to the data cut-off for this submission (April 2, 2002 for Protocol 016.0023; 016.0012 is closed). Results are described as statistically significant when p-values are < 0.05 (2-sided). Confidence intervals are 95% (2-sided), based on raw estimates for standard deviation. No adjustments were made for multiplicity.

Patients in Protocol 016.0012 could remain on study after stopping drug. For the analyses in this report, only visits measured while on drug (on treatment) are included, in order to render the analyses analogous to those done for the late-stage RA studies. Previous analyses submitted in earlier filings for Protocol 016.0012 have established that comparisons between groups were similar whether these visits were included or excluded.

As with the late-stage RA studies, the HAQ disability index is presented over time during the 12 months that constitute the blinded phase of Protocol 016.0012 as raw score and percent change in score relative to baseline for each treatment group. Both observed values and LOCF values are summarized. In addition, the following analyses of patients are presented over time:

- Proportion with HAQ = 0 (no disability)
- Proportions with HAQ improvement from baseline > 0.25, > 0.50, and $>$ 1.0 units (0.22 units is considered clinically important)

For Protocol 016.0012, the 8 subscales and 2 summary scores of the SF-36 questionnaire are presented for all patients as raw score and change (both observed and LOCF) as well as for the proportions of patients with improvements > 5 units and > 10 units in each scale (10 units = one standard deviation, considered clinically important) and with values.

Results were calculated relative to baseline information from Protocol 016.0012 and over time in Protocols 016.0012 through 24 months and then in Protocol 016.0023. Results are presented for the following 3 subsets:

- Patients who received MTX in Protocol 016.0012
- Patients who received 10 mg etanercept in Protocol 016.0012
- Patients who received 25 mg etanercept in Protocol 016.0012

The progression of patients from Protocol 016.0012 to Protocol 016.0023 and their inclusion in the long-term Supportive Tables are illustrated graphically in Table 19.

Table 19 : Early-Stage RA Patients Treated with Etanercept 25 mg Twice Weekly – Evaluated for Physical Function

Studies (Early RA)		Number Originally Enrolled	Number Completed Open-Label Year 2	Number Enrolled Open-Label 016.0023	Number Included Long-Term Tables
016.0012 Blinded Year 1 Open-Label Year 2	10 mg Etanercept	208	163	143	
	25 mg Etanercept	207	162	163	161
	Methotrexate	217	104	161	
	Totals ->	**N=632**	N=429	**N=467**	
016.0023 Open-Label Duration 2 - 5 Years	**25 mg Etanercept**	467			

B. Health Assessment Questionnaire Results

1. HAQ Results At Years One and Two

Protocol 016.0012 (Year 1)

In Protocol 016.0012, 632 patients were treated with blinded study drug: 207 patients in the etanercept 25 mg group, 208 patients in the etanercept 10 mg group, and 217 patients in the MTX group.

Table 20 summarizes the results for the HAQ disability index over time in the 12-month active-controlled study, using the LOCF analysis.

Table 20 : Protocol 016.0012 Early-Stage, Year 1: HAQ Disability Index (LOCF Analysis)

		Etanercept		P-values*		
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 10 mg	MTX vs 25 mg	10 mg vs 25 mg
Mean value†						
Baseline	1.4	1.4	1.5			
Week 2	1.3	1.1	1.1			
Month 1	1.2	1.0	1.0			
Month 3	0.9	0.9	0.8			
Month 6	0.8	0.9	0.7			
Month 8	0.7	0.9	0.7			
Month 10	0.7	0.9	0.7			
Month 12	0.7	0.9	0.7			
Mean improvement from baseline						
Week 2	0.09	0.30	0.38	< 0.0001	< 0.0001	0.0030
Month 1	0.19	0.42	0.47	< 0.0001	< 0.0001	0.1449
Month 3	0.52	0.57	0.65	0.6028	0.0291	0.1015
Month 6	0.66	0.59	0.70	0.6869	0.1551	0.0728
Month 8	0.70	0.58	0.72	0.2531	0.3478	0.0408
Month 10	0.70	0.56	0.70	0.0945	0.5654	0.0273
Month 12	0.72	0.55	0.71	0.0176	0.7442	0.0080
Mean % improvement from baseline						
Week 2	6%	24%	29%	< 0.0001	< 0.0001	0.0411
Month 1	13%	33%	37%	< 0.0001	< 0.0001	0.5516
Month 3	36%	44%	49%	0.0484	0.0025	0.2941
Month 6	46%	43%	50%	0.8349	0.1260	0.1928
Month 8	48%	41%	52%	0.7744	0.1590	0.0953
Month 10	49%	40%	53%	0.3686	0.1813	0.0280
Month 12	50%	38%	53%	0.0956	0.3000	0.0080

* P-value determined by ANOVA (model with factors for treatment, disease duration, and their interaction; see

† Range: 0 = best assessment, 3 = worst assessment.

Patients treated with either 10 mg or 25 mg etanercept demonstrated more rapid improvements in their HAQ scores compared to patients treated with MTX, as shown by the mean percent improvements from baseline through Month 3. The difference between groups was significant as early as 2 weeks after initiation of study drug, although the difference disappeared by Month 6. Patients treated with 25 mg etanercept have consistently higher levels of improvements than patients treated with 10 mg etanercept, especially at later time points in the study. In addition, while comparisons across studies must be done with caution, patients with early RA who were treated with 25 mg etanercept demonstrated numerically higher reductions in HAQ scores than observed in etanercept-treated patients with late-stage disease.

The 95% confidence intervals for change at Month 12 from baseline in HAQ score and the differences in that change between the MTX and 25 mg etanercept groups and between the 10 mg and 25 mg etanercept groups are shown in Table 21. The confidence interval for the difference between the etanercept 25 mg and either MTX or etanercept 10 mg overlapped zero. All three treatment groups of early RA patients in Protocol 016.0012 exceeded the clinically important improvement (change of 0.22 units in the HAQ).

Table 21 : Protocol 016.0012 Early-Stage, Year 1: HAQ Disability Index – Change from Baseline to Month 12 – Observed and LOCF (95% Confidence Intervals)

		Etanercept		Difference	
	MTX (n = 176)	10 mg (n=159)	25 mg (n = 177)	MTX vs 25 mg	10 mg vs 25 mg
Observed analysis:					
Mean change from baseline to Month 12	0.80	0.64	0.77	0.03	-0.13
(95% Confidence Interval)	(0.70, 0.90)	(0.54, 0.74)	(0.68, 0.86)	(-0.10, 0.16)	(-0.27, 0.01)
	MTX (n = 217)	10 mg (n=208)	25 mg (n = 207)	MTX vs 25 mg	10 mg vs 25 mg
LOCF analysis:					
Mean change from baseline to Month 12	0.72	0.55	0.71	0.01	-0.16
(95% Confidence Interval)	(0.63, 0.81)	(0.46, 0.64)	(0.63, 0.79)	(-0.11, 0.13)	(-0.28, -0.04)

Additional measurements of the HAQ disability index in Protocol 016.0012 included the number of patients who achieved a zero HAQ score and those patients who achieved improvements ≥ 0.25, ≥ 0.5, or ≥ 1.0 units in their HAQ scores. More patients treated with 25 mg etanercept reached all of the above benchmarks of improvement at 12 months, compared with patients treated with 10 mg etanercept. In addition, while comparisons across studied must be interpreted with caution, higher proportions of patients with early-stage RA who were treated with 25 mg etanercept achieved these previously-defined important improvements in HAQ scores than did etanercept-treated patients in studies of late-stage disease.

The results of these additional measurements at 12 months in the active-controlled study, using the qualified LOCF analysis are shown in Table 22.

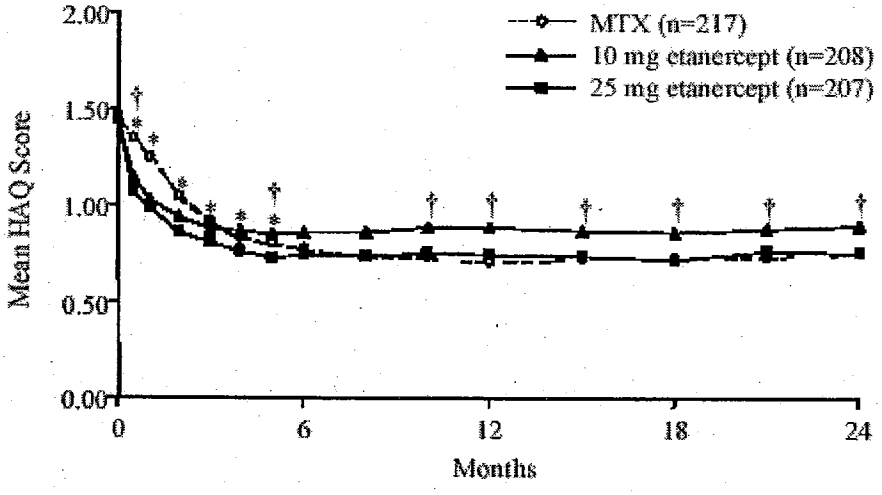
More patients treated with 25 mg etanercept reached all of the above benchmarks of improvement at 12 months, compared with patients treated with 10 mg etanercept. In addition, while comparisons across studies must be interpreted with caution, higher proportions of patients with early RA who were treated with 25 mg etanercept achieved these previously-defined important improvements in HAQ scores than did etanercept-treated patients in studies of late-stage disease.

Table 22 : Protocol 016.0012 Early-Stage, Year 1: Additional HAQ Assessments at 12 Months (Qualified LOCF Analysis)

		Etanercept		P-values*		
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 10 mg	MTX vs 25 mg	10 mg vs 25 mg
Patients with zero HAQ score	26%	19%	29%	0.1044	0.3991	0.0148
Patients with decrease of ≥ 0.25 in HAQ	75%	65%	82%	0.0280	0.1023	0.0002
Patients with decrease of ≥ 0.5 in HAQ	60%	54%	60%	0.2070	0.9993	0.2127
Patients with decrease of ≥ 1.0 in HAQ	35%	28%	32%	0.1129	0.5630	0.3195

* P-value determined by likelihood ratio chi-square test. Tests adjusting for disease duration (Cochran-Mantel-Haenszel row means test) yielded identical statistical conclusions.

Patients in all treatment groups maintained their improvements from baseline HAQ scores. Additionally, patients in the 25 mg etanercept group sustained higher percent improvements compared with patients in the 10 mg etanercept group, as shown in Figure 4. Mean HAQ scores for the 3 treatment groups are shown over time in Table 23.



* p-value < 0.05 for % change, 25 mg vs. MTX
† p-value < 0.05 for % change, 25 mg vs. 10 mg
Note: Standard errors for HAQ score over time for each group were consistently no greater than 0.05

Figure 4 : Protocol 016.0012 Early-Stage, Years 1 and 2: Mean HAQ Scores Over Time

Table 23 : Protocol 016.0012 Early-Stage, Year 2: HAQ Disability Index (LOCF Analysis)

		Etanercept		P-values*		
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 10 mg	MTX vs 25 mg	10 mg vs 25 mg
Mean value†						
Baseline‡	1.4	1.4	1.5			
Month 12	0.7	0.9	0.7			
Month 15	0.7	0.8	0.7			
Month 18	0.6	0.7	0.6			
Month 21	0.6	0.7	0.6			
Month 24	0.6	0.7	0.6			
Mean improvement from baseline						
Month 12**	0.72	0.55	0.71	0.0176	0.7442	0.0080
Month 15	0.71	0.58	0.71	0.0992	0.8099	0.0632
Month 18	0.71	0.59	0.73	0.1196	0.6995	0.0562
Month 21	0.70	0.57	0.69	0.0731	0.8693	0.1093
Month 24	0.68	0.56	0.70	0.1485	0.7583	0.0849
Mean % improvement from baseline						
Month 12**	50%	38%	53%	0.0956	0.3000	0.0080
Month 15	51%	38%	52%	0.0463	0.7933	0.0267
Month 18	49%	41%	53%	0.1213	0.4324	0.0219
Month 21	49%	36%	50%	0.0100	0.8312	0.0061
Month 24	47%	35%	51%	0.0392	0.5622	0.0095

* P-value determined by ANOVA (model with factors for treatment, disease duration, and their interaction; see

† Range: 0 = best assessment, 3 = worst assessment.

‡ Original baseline of Protocol 016.0012.

** Note: Month 12 results in this table are the same as those presented in the controlled study Month 12 results in the Supportive Tables for the controlled study differ slightly from results in the long-term Supportive Tables due to differences in the datasets for controlled and long-term results.

The 25 mg etanercept group achieved significantly greater improvements at the end of the 1-year controlled study and sustained those improvements throughout the second year of the study, compared with patients in the 10 mg etanercept group. The table below summarizes the results of additional measurements (zero HAQ scores and improvements ≥ 0.25, ≥ 0.5, or ≥ 1.0 units) in the second year of the active controlled study, using the qualified LOCF analysis.

At the end of Year 2 (Table 24), 51% of the patients in the 10 mg etanercept group had improvements of ≥ 0.5 units in the HAQ score compared to 63% in the 25 mg etanercept group. The 25 mg etanercept group was significantly better than the 10 mg etanercept group for 3 of the 4 benchmarks in the table. Approximately one-third of all patients in the etanercept 25 mg had ≥ 1.0-unit improvements in their HAQ scores.

Table 24 : Protocol 016.0012 Early-Stage, Year 2: Additional HAQ Assessments at 24 Months (Qualified LOCF Analysis)

		Etanercept		P-values*		
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 10 mg	MTX vs 25 mg	10 mg vs 25 mg
Patients with zero HAQ score	24%	18%	27%	0.1843	0.4659	0.0421
Patients with decrease of ≥ 0.25 in HAQ	69%	62%	77%	0.1001	0.0573	0.0005
Patients with decrease of ≥ 0.5 in HAQ	54%	51%	63%	0.6095	0.0634	0.0192
Patients with decrease of ≥ 1.0 in HAQ	34%	27%	33%	0.1079	0.7849	0.1869

* P-value determined by likelihood ratio chi-square test. Tests adjusting for disease duration (Cochran-Mantel-Haenszel row means test) yielded identical statistical conclusions.

C. Sensitivity Analysis

As with the late-stage RA patients in Protocols 016.0009 and 016.0014, an additional set of analyses was performed to assess sustained improvement in each individual patient in Protocol 016.0012. In these analyses, a stringent set of criteria was applied: a patient in any treatment group was considered to have achieved "sustained improvement" of ≥ 0.25, ≥ 0.5, and ≥ 1.0 units of the HAQ only if the patient met ALL of the following conditions:

- Receiving treatment at the 12-month time point.
- Achieved the described level of improvement (0.25, 0.5, 1.0 HAQ units) at the 12-month time point.
- Achieved the described level of improvement at the 24-month visit and were improved or missing at all visits between 12 months and 24 months.

These analyses were performed in 2 ways: sustained, which required patients to be on study and receiving etanercept, with improved HAQ values at the 24-month visit and sustained (LOCF), which allowed LOCF of last available visit to achieve sustained improvement. Observed sustained improvement patterns are visually displayed for patients in each treatment group. Classification of patients for sensitivity analysis is summarized in Table 25.

Table 25 : Classification of Patients for Sensitivity Analysis

Enbrel Group

Sustained – Achieved improvement at 24 months with improved or missing evaluations at all interim visits between 12 and 24 months

Sustained (LOCF) – Responder at last available evaluation

Table 26 : Protocol 016.0012 Early-Stage : Sustained HAQ Results From Baseline through Year 2

		Etanercept		P-values*	
	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs. 25 mg	10 mg vs 25 mg
Sustained analysis:					
Patients with decrease of ≥ 0.25 in HAQ (n[%])	86/217 (40%)	88/208 (42%)	117/207 (57%)	0.0006	0.0044
Patients with decrease of ≥ 0.50 in HAQ (n[%])	69/217 (32%)	72/208 (35%)	85/207 (41%)	0.0550	0.1890
Patients with decrease of ≥ 1.0 in HAQ (n[%])	45/217 (21%)	35/208 (17%)	37/207 (18%)	0.4637	0.7697
Sustained (LOCF) analysis:					
Patients with decrease of ≥ 0.25 in HAQ (n[%])	110/217 (51%)	104/208 (50%)	128/207 (62%)	0.0243	0.0176
Patients with decrease of ≥ 0.50 in HAQ (n[%])	91/217 (42%)	80/208 (38%)	91/207 (44%)	0.6954	0.2734
Patients with decrease of ≥ 1.0 in HAQ (n[%])	54/217 (25%)	38/208 (18%)	42/207 (20%)	0.2964	0.6206

* P-value determined by Fisher's exact test.

Table 26 demonstrates that significantly more patients in the 25 mg etanercept group had a sustained decrease of ≥ 0.25 units in the HAQ score for 2 years, using both the sustained and sustained (LOCF) analyses, compared with the 10 mg etanercept group. Furthermore, higher proportions of patients with early RA who received 25 mg etanercept in this study had high levels of improvement than patients with late-stage RA who received 25 mg etanercept.

2. Long-term HAQ Results At Years Three and Four

After all patients had received open-label treatment with the originally assigned medication until completion of a second year in Protocol 016.0012, all patients who chose to enroll in the long-term extension study, Protocol 016.0023, received open-label etanercept at a dose of 25 mg SC twice weekly. Of note, during the long-term study, patients were allowed to decrease or discontinue their use of corticosteroids. Of the 632 patients in the controlled study, 468 chose to enroll in Protocol 016.0023. One patient withdrew from the extension study prior to collection of efficacy data; therefore, data for 467 patients are included in results for Protocol 016.0023.. At the end of 2 years in Protocol 016.0023, patients on 25 mg etanercept had received up to 4 years of etanercept therapy.

Table 27 summarizes the HAQ disability scores and improvements from baseline of Protocol 016.0023 as well as results of additional measurements (zero HAQ scores and improvements ≥ 0.25, ≥ 0.5, or ≥1.0 units) at the end of the second year of the extension study, using an observed analysis for patients originally randomized to 25 mg etanercept.

Table 27 : Protocol 016.0023 Early-Stage: 25 mg Etanercept Patients

Mean Observed HAQ Results From Baseline through Data Cut-off

	Open-label 25 mg etanercept						
	Baseline* (n = 161)	6 mo. (n = 154)	12 mo. (n = 148)	16 mo. (n = 142)	20 mo. (n = 133)	24 mo. (n = 109)	Last Visit (n = 161)
Mean HAQ score†	0.7	0.7	0.7	0.7	0.7	0.8	0.8
Mean improvement from baseline in Protocol 016.0012 in HAQ score	0.80	0.78	0.79	0.72	0.77	0.76	0.70
Mean % improvement from baseline in Protocol 016.0012 in HAQ score	58%	54%	56%	50%	51%	50%	49%
Patients with zero HAQ score	28%	30%	26%	26%	23%	23%	23%
Patients with decrease of ≥ 0.25 in HAQ	86%	82%	83%	80%	83%	81%	80%
Patients with decrease of ≥ 0.5 in HAQ	73%	69%	68%	67%	67%	71%	66%
Patients with decrease of ≥ 1.0 in HAQ	39%	41%	39%	37%	33%	37%	34%

* Baseline of Protocol 016.0023.
† Range: 0 = best assessment; 3 = worst assessment.

During the long-term Protocol 016.0023, patients originally randomized to 25 mg etanercept maintained their improvements from baseline HAQ scores. The majority of patients exceeded the "clinically important" standard of a 0.22-unit decrease in the HAQ score, as well as an even higher standard, a >0.50-unit decrease in the HAQ. Many patients achieved even higher benchmarks of improvement.

Table 28 compares the observed and LOCF HAQ scores among patients with early-stage RA treated with etanercept 25 mg twice weekly for 48 months (24 months in Protocol 016.0012 and 24 months in Protocol 016.0023). Approximately two-thirds of patients entering study 16.0023 remained on study at 24 months. The sponsor did not calculate LOCF data during the second 24 months of study 016.0023.

The mean HAQ at the original baseline was 1.45, and was 0.63 at 24 months, a reduction of 0.82, and the mean HAQ at the last visit and at 48 months for the patients remaining in the study was 0.75, a reduction of 0.70 at 4 years. In addition, at 4 years 80% achieved a reduction in HAQ $\geq$ 0.25%, 60% achieved a reduction in HAQ $\geq$ 0.50%, and 30% achieved a reduction in HAQ $\geq$ 1.0%. Over 20% of patients achieved and maintained a HAQ score of '0'.

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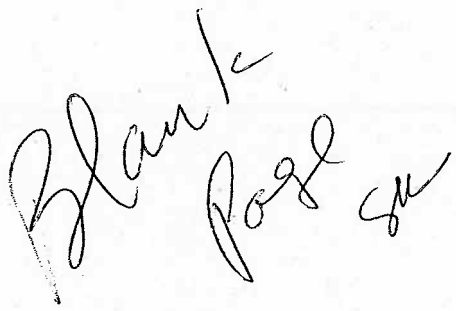
Table 28 : Comparison of Observed and LOCF HAQ Results Among Patients with Early-Stage RA Treated With Etanercept 25 mg Twice Weekly and Rolled Over From Study 016.0012 Into 016.0023

	Study 016.0012							Study 016.0023						
	Months							Months						
	Baseline 016.0012	6	12	15	18	21	24	Baseline 016.0023	6	12	16	20	24	Last Visit
Observed n =	207	193	179	172	165	160	152	161	154	148	142	133	109	161
HAQ mean	1.45	0.72	0.67	0.66	0.64	0.64	0.63	0.65	0.67	0.67	0.73	0.70	0.75	0.75
HAQ = 0 %	3	28	33	33	30	30	29	28	30	26	26	23	23	23
Improvement														
HAQ ≥ 0.25 %		83	87	84	84	86	87	86	82	83	80	83	81	80
HAQ ≥ 0.50 %		65	65	66	70	75	74	73	69	68	67	67	71	66
HAQ ≥ 1.0 %		33	34	38	40	41	39	39	41	39	37	33	37	34
LOCF n =	207	207	207	207	207	207	207	These data are not available						
HAQ mean	1.45	0.75	0.74	0.74	0.72	0.76	0.75							
HAQ = 0	3	27	29	30	29	27	27							
Improvement														
HAQ ≥ 0.25 %		82	83	80	80	80	81							
HAQ ≥ 0.50 %		63	60	60	61	64	64							
HAQ ≥ 1.0 %		32	32	34	35	34	33							



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VI. Comparison of Improvement in HAQ Score of Early-Stage and Late-Stage RA Patients

While interpretation of results across studies must be done with caution, it is instructive to examine similarities and differences in HAQ responses among patients enrolled in early-stage and late-stage RA. Patients with early-stage RA had baseline mean HAQ score of 1.61 and those with late-stage RA mean HAQ score of 1.45. Based on observed data at both the first and second year time-points, similar proportions of early and late-stage RA patients achieved ≥ 0.25 reduction, ≥ 0.50 reduction, and 30% of patients achieved ≥ 1.00 reduction in HAQ score. At the end of year one and year two, a higher proportion of early-stage etanercept-treated patients achieved HAQ score of '0', compared to late-stage patients (33% vs. 19% for year 1; 29% vs. 22% for year 2) (Table 29).

Table 29 : Comparison of Early-Stage and Late-Stage Improvement in HAQ Score (Mean Observed Data)

Patients with HAQ score	Etanercept 25 mg			
	Percentage of Patients At 1 Year		Percentage of Patients At 2 Years	
	Early Stage RA [1]	Late Stage RA [2]	Early Stage RA [1]	Late Stage RA [2]
Mean % improvement	59%	49%	59%	53%
Score zero	59/179 (33%)	11/59 (19%)	44/152 (29%)	8/37 (22%)
Improvement				
Decrease ≥ 0.25	156/179 (87%)	47/59 (80%)	132/152 (87%)	31/37 (84%)
Decrease ≥ 0.50	116/179 (65%)	37/59 (63%)	113/152 (74%)	26/37 (70%)
Decrease ≥ 1.0	64/179 (36%)	18/59 (31%)	60/152 (39%)	15/37 (41%)

1 Patients treated with etanercept 25 mg in both Protocols 016.0012 and 016.0023
2 Patients treated with etanercept 25 mg in both Protocols 016.0009 and 016.0018

Analysis of responses using LOCF imputation in Table 30 suggests a higher level of reduction in HAQ scores at both first and second year time-points for early-stage RA compared to late-stage RA.

Table 30 : Comparison of Early-Stage and Late-Stage Improvement in HAQ Score (LOCF Data)

	Etanercept 25 mg			
	Percentage of Patients At 1 Year		Percentage of Patients At 2 Years	
Patients with HAQ score	**Early Stage RA [1]**	**Late Stage RA [2]**	**Early Stage RA [1]**	**Late Stage RA [2]**
Mean % improvement	53	40	51	39
Score zero	29	15	27	13
Improvement				
Decrease ≥ 0.25	83	68	81	71
Decrease ≥ 0.50	60	52	64	59
Decrease ≥ 1.0	32	25	33	31

1 Patients treated with etanercept 25 mg in both Protocols 016.0012 and 016.0023
2 Patients treated with etanercept 25 mg in both Protocols 016.0009 and 016.0018

In **Figure 5**, patients with early RA who received 25 mg etanercept over a 12-month period are compared with patients with late-stage RA from the two 6-month placebo-controlled studies. Patients who received 25 mg etanercept in all 3 controlled studies had improvement in their HAQ scores, that was observed as early as 3 months.

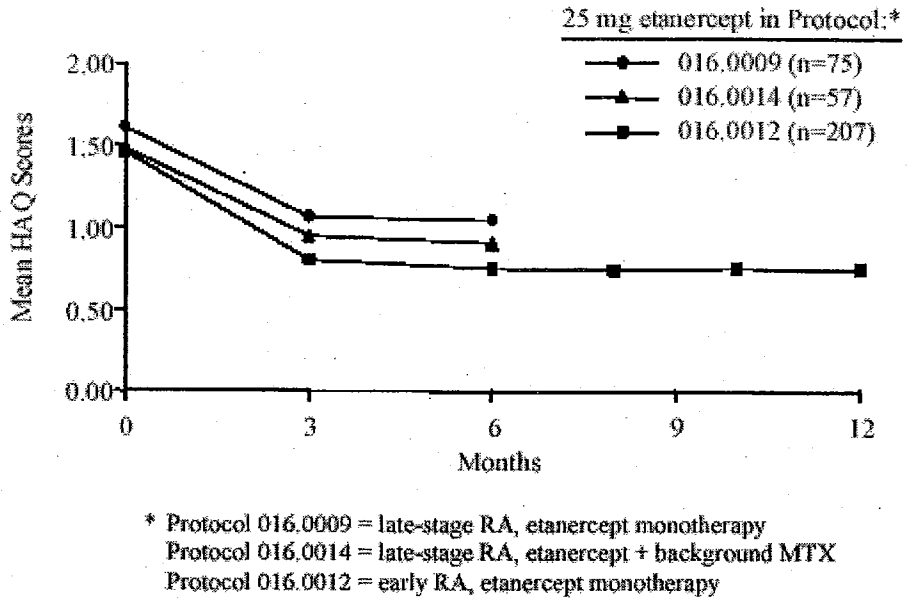

Figure 5 : Late-stage and Early RA: Mean HAQ Scores in Controlled Studies

A. Evaluation of HAQ Scores Among Patients at Withdrawal

Analysis of study results for patients remaining in the trial may be biased if patients who drop out were experiencing lack of efficacy. Therefore, we performed evaluations to determine whether patients who withdrew during the second year of etanercept monotherapy were dropping out due to loss of efficacy. Comparisons were made of the improvement in HAQ scores among patients continuing therapy and those discontinuing therapy and the proportion of patients discontinuing due to lack of efficacy during the first and the second halves of the second year. While the numbers of patients are small, some trends are suggested (Table 31; Table 32).

Patients with both late-stage and early-stage RA who discontinued had similar baseline HAQ scores compared to those patients remaining in the studies (higher in 2 cases; lower in 2 others) Last visit HAQ scores tended to be higher among all patients discontinuing than among patients continuing in studies. HAQ scores at discontinuation were generally similar among patients experiencing lack of efficacy and those not reporting lack of efficacy. Patients discontinuing therapy generally had lesser reductions in their HAQ scores than those remaining in the study and smaller proportions achieving a reduction of ≥ 0.25. Thus, patients discontinuing treatment generally had higher HAQ scores than those remaining and fewer had achieved a clinically meaningful improvement compared to those remaining. However, the differences are small and the majority of the dropouts had experienced clinically meaningful improvement in their HAQ scores.

Table 31 : Comparison of HAQ Scores Among Late-Stage Patients Remaining and Patients Discontinued During the Second Year in Study 16.0009 Treated With Etanercept 25 mg Twice Weekly

	Months 12 to 18			Months 18 to 24		
	Patients Within Study	Discontinuations		Patients Within Study	Discontinuations	
		All	Excludes LOE *		All	Excludes LOE *
Number Patients (beginning-> end of period)	59->56	7	6	56->37	2	2
HAQ Baseline (mean)	1.61	1.46	1.44	1.61	2.06	2.06
HAQ Last visit (mean)	0.88-0.91	1.11	1.00	0.85-0.88	1.38	1.38
HAQ Decrease Last visit (mean)	0.70-0.73	0.36	0.44	0.73-0.76	0.69	0.69
HAQ % with Decrease ≥ 0.25	79-80%	57%	67%	79-84%	50%	50%

* = Lack of efficacy

Table 32 : Comparison of HAQ Scores Among Early-Stage Patients Remaining and Patients Discontinued During the Second Year in Study 16.0012 Treated With Etanercept 25 mg Twice Weekly

	Months 12 to 18			Months 18 to 24		
	Patients Within Study	Discontinuations		Patients Within Study	Discontinuations	
		All	Excludes LOE *		All	Excludes LOE *
Number Patients (beginning-> end of period)	179->165	14	10	165->152	10	9
HAQ Baseline (mean)	1.45	1.36	1.20	1.45	1.61	1.57
HAQ Last visit (mean)	0.64-0.67	1.01	0.70	0.63-0.64	0.89	0.79
HAQ Decrease Last visit (mean)	0.78-0.81	0.35	0.50	0.81-0.82	0.73	0.73
HAQ % with Decrease ≥ 0.25	84-87%	64%	70%	84-87%	80%	78%

* = Lack of efficacy

VII. Short-Form Health Survey-36 Outcomes (SF-36)

Patient responses on the SF-36, a generic health-related physical-function instrument, are submitted as supportive data in the physical functioning claim for etanercept. The primary source for SF-36 data is from patients with early RA who were treated with etanercept or MTX in active-controlled Protocol 016.0012. Patients recorded their answers on the SF-36 for 2 years in that study; no data were collected from the long-term extension study, Protocol 016.0023. Supportive SF-36 data are also available from a subset of patients with late-stage RA who were treated with etanercept or placebo in Protocol 016.0009. No additional controlled or long-term SF-36 data are available from patients with late-stage RA.

A. SF-36 Results in Late-Stage RA Controlled Study

Protocol 016.0009 – Etanercept as Monotherapy

In Protocol 016.0009, patient responses on the SF-36 instrument were added to the study evaluations after the study was started; therefore, only a subset of 47 patients had baseline scores: 18 patients in the 25 mg etanercept group, 16 patients in the 10 mg etanercept group, and 13 patients in the placebo group. Table 33 summarizes the mean physical component summary (PCS) and mental component summary (MCS) scores and the mean change from baseline over time for this subset of patients in the 6-month controlled study, using an LOCF analysis.

Table 33 : Protocol 016.0009 Late-Stage: Improvements in SF-36 Physical and Mental Component Summaries (LOCF Analysis)

	Physical Component Summary (PCS)					Mental Component Summary (MCS)				
		Etanercept		P-values			Etanercept		P-values	
Parameter	Placebo (n = 13)	10 mg (n = 16)	25 mg (n = 18)	Pbo vs 10 mg	Pbo vs 25 mg	Placebo (n = 13)	10 mg (n = 16)	25 mg (n = 18)	Pbo vs 10 mg	Pbo vs 25 mg
Mean values:*										
Baseline	27.8	26.5	29.0			47.1	47.5	46.5		
Month 1	27.1	31.7	31.4			50.1	48.9	46.1		
Month 3	27.3	32.1	30.5			52.7	51.1	51.5		
Month 6	25.2	33.4	33.9			53.6	50.0	49.0		
Mean change from baseline:										
Month 1	-0.7	5.2	2.4	0.015	0.179	3.0	1.4	-0.3	0.604	0.272
Month 3	-0.4	5.7	1.5	0.037	0.480	5.6	3.5	5.0	0.603	0.892
Month 6	-2.6	6.9	5.0	0.006	0.022	6.5	2.5	2.6	0.252	0.247
(Month 6 – 95% C.I.)	(-4.7, -0.5)	(2.4, 11.4)	(0.1, 9.9)			(1.9, 11.1)	(-2.9, 7.9)	(-0.5, 5.7)		

* 0 = worst; 100 = best; 50 = U.S. norm.

Patients in all treatment groups of this study had reduced (abnormal) PCS scores at baseline compared to U.S. norms (U.S. norms = 50, SD=10). However, by Month 6, both the 10 mg and 25 mg etanercept groups had significantly better PCS scores than the placebo group (p = 0.006 and 0.022, respectively). In contrast to the PCS, patients in all treatment groups of Protocol 016.0009 had MCS scores that were near U.S. norms at baseline. Improvements in MCS scores were similar among treatment groups during the 6-month study, and none of the treatment groups demonstrated decreases in MCS scores.

B. SF-36 Results in Early-Stage RA Controlled Study

Protocol 016.0012 (Year 1)

Six hundred thirty-two patients were treated with blinded study drug during the first year of Protocol 016.0012: 207 patients in the etanercept 25 mg group, 208 patients in the etanercept 10 mg group, and 217 patients in the MTX group. Table 34 summarizes the mean PCS and MCS scores and the mean change from baseline over time in the 12-month controlled study, using an LOCF analysis for the normed scores (described in Appendix 3).

Table 34 : Protocol 016.0012 Early-Stage, Year 1: Improvements in SF-36 Physical and Mental Component Summaries (LOCF Analysis)

	Physical Component Summary (PCS)					Mental Component Summary (MCS)				
		Etanercept		P-values*			Etanercept		P-values	
Parameter	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg
Mean values:†										
Baseline	28.8	28.2	28.2			47.3	46.9	46.4		
Month 3	37.1	36.6	38.8			52.4	51.3	50.9		
Month 6	39.4	36.8	39.3			52.7	52.0	51.1		
Month 12	39.7	36.4	39.5			52.6	50.6	50.8		
Mean change from baseline:										
Month 3	8.2	8.4	10.6	0.007	0.043	5.0	4.4	4.5	0.530	0.959
Month 6	10.6	8.6	11.1	0.279	0.025	5.3	5.1	4.7	0.623	0.920
Month 12	10.8	8.3	11.3	0.492	0.005	5.2	3.8	4.4	0.404	0.504
(Month 12 – 95% C.I.)	(9.9, 12.3)	(6.8, 9.8)	(9.9, 12.7)			(3.6, 6.8)	(2.2, 5.4)	(2.8, 6.0)		

* P-value determined by ANOVA (model with factors for treatment, disease duration, and their interactions, see

† 0 = worst; 100 = best; 50 = U.S. norm.

Patients with early RA in Protocol 016.0012 had low PCS scores at baseline that were similar to the late-stage RA population. However, PCS scores in early RA patients in all treatment groups during the first year of this study were higher than those seen in the late-stage RA population. Patients in the 25 mg etanercept group improved more from Month 3 forward, than patients in the 10 mg group (p = 0.005 at Month 12), but similar to patients in the MTX group. Patients in all treatment groups had MCS scores that were

near U.S. norms at baseline; all three treatment groups experienced improvements in MCS of approximately 4% - 5%.

While all groups demonstrated improvements in MCS scores, no significant differences between groups were seen. A change of 10 units in the normed sum of the SF-36 represents one standard deviation. Analyses were conducted comparing the percent of patients with >5- and >10-unit improvements in SF-36 scores as well as the percent of patients with normed scores > 50 units. Results are shown in Table 35, using the qualified LOCF analysis, where a missing value was counted as "no improvement" if it was due to discontinuation for lack of efficacy.

Table 35 : Protocol 016.0012 Early-Stage RA Year 1: Percent Patients with Improvements of ≥ 5 and ≥ 10 units or Normed Score ≥ 50 units in SF-36 PCS and MCS (LOCF Analysis)

	Physical Component Summary (PCS)					Mental Component Summary (MCS)				
		Etanercept		P-values*			Etanercept		P-values*	
Patients with	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg
≥ 5-unit improvement:										
Month 3	61%	58%	66%	0.252	0.092	40%	41%	42%	0.761	0.888
Month 6	66%	61%	65%	0.804	0.380	44%	46%	41%	0.509	0.343
Month 12	66%	57%	69%	0.623	0.012	41%	41%	40%	0.769	0.795
≥ 10-unit improvement:										
Month 3	37%	37%	50%	0.007	0.009	28%	26%	26%	0.639	0.934
Month 6	48%	48%	51%	0.630	0.590	31%	30%	29%	0.593	0.770
Month 12	52%	44%	54%	0.749	0.056	30%	26%	26%	0.317	0.934
Normed score ≥ 50 units:										
Baseline	1%	2%	< 1%	0.326	0.164	49%	48%	45%	0.478	0.655
Month 3	13%	14%	23%	0.009	0.015	67%	63%	63%	0.388	0.869
Month 6	22%	19%	27%	0.237	0.057	68%	65%	63%	0.285	0.656
Month 12	24%	15%	23%	0.765	0.031	68%	59%	60%	0.114	0.795

* P-values determined by likelihood ratio chi-square test.

PCS scores improved in all treatment groups, as shown by the proportions of patients with 5- and 10-unit improvements. However, at 12 months, more patients in the 25 mg etanercept group achieved 5-unit and 10-unit improvements in the PCS, compared with the 10 mg etanercept group. Furthermore, more patients in the 25 mg etanercept group were at or above the median of the U.S. population for the PCS score at 12 months, compared with the 10 mg etanercept group. Whereas the MCS scores were near the median of the U.S. population (50 units) at baseline, less improvement in these scores would be expected. Improvements were seen in all treatment groups but were not significantly different among the groups.

Protocol 016.0012 (Year 2)

After all patients had received blinded treatment with MTX or etanercept for at least 12 months in Protocol 016.0012, patients who remained in the study continued to receive open-label treatment with the originally assigned medication until completion of a second year. Table 36 summarizes the mean PCS and MCS scores and the mean change from baseline over time in Year 2 of the study, using an LOCF analysis.

Table 36 : Protocol 016.0012 Early-Stage, Year 2: Improvements in SF-36 Physical and Mental Component Summaries (LOCF Analysis)

	Physical Component Summary (PCS)					Mental Component Summary (MCS)				
		Etanercept		P-values*			Etanercept		P-values*	
Parameter	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg
Mean values:†										
Baseline	28.8	28.2	28.2			47.3	46.9	46.4		
Month 12	39.7	36.4	39.5			52.6	50.6	50.8		
Month 18	39.3	36.8	39.5			52.3	50.8	51.0		
Month 24	38.7	36.3	39.4			51.5	50.5	51.2		
Mean change from baseline:										
Month 12‡	10.8	8.3	11.3	0.492	0.005	5.2	3.8	4.4	0.404	0.504
Month 18	10.4	8.6	11.3	0.285	0.032	5.0	4.0	4.6	0.759	0.655
Month 24	9.9	8.2	11.2	0.315	0.041	4.1	3.6	4.8	0.734	0.593
(Month 24 – 95% C.I.)	(8.4, 11.4)	(6.7, 9.7)	(9.8, 12.6)			(2.6, 5.6)	(1.8, 5.4)	(3.1, 6.5)		

* P-value determined by ANOVA (model with factors for treatment, disease duration, and their interactions, see

† 0 = worst; 100 = best; 50 = U.S. norm.

‡ Month 12 results in the Supportive Tables for the controlled study differ slightly from results in the long-term Supportive Tables due to differences in the datasets for controlled and long-term results.

Improvements in the PCS score were sustained during the second year of treatment. The 25 mg etanercept group had higher improvement in the PCS at the end of the second year, compared to the 10 mg group. Smaller improvements in the MCS scores were sustained during Year 2 of the study.

As in Year 1 of the active-controlled study, analyses were conducted of percent of patients with ≥ 5- and ≥ 10-unit improvements in SF-36 scores as well as percent of patients with normed scores ≥ 50 units. Results are shown in Table 37, using the qualified LOCF analysis, where a missing value was counted as "no" if it was due to discontinuation for lack of efficacy.

Table 37 : Protocol 016.0012 Early-Stage, Year 2: Percent Patients with Improvements of 5 and 10 units or Normed Scores ≥ 50 units in SF-36 PCS and MCS (LOCF Analysis)

	Physical Component Summary (PCS)					Mental Component Summary (MCS)				
		Etanercept		P-values			Etanercept		P-values	
Patients with	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg	MTX (n = 217)	10 mg (n = 208)	25 mg (n = 207)	MTX vs 25 mg	10 vs 25 mg
≥ 5-unit improvement:										
Month 12*	66%	57%	69%	0.623	0.012	41%	41%	40%	0.769	0.795
Month 18	65%	60%	66%	0.718	0.199	42%	41%	42%	0.859	0.967
Month 24	60%	56%	69%	0.048	0.005	39%	38%	43%	0.425	0.297
≥ 10-unit improvement:										
Month 12*	52%	44%	54%	0.749	0.056	30%	26%	26%	0.317	0.934
Month 18	49%	43%	51%	0.627	0.105	30%	29%	29%	0.666	0.938
Month 24	46%	39%	50%	0.341	0.020	26%	28%	31%	0.202	0.433
Normed score ≥ 50 units:										
Baseline	1%	2%	< 1%	0.326	0.164	49%	48%	45%	0.478	0.655
Month 12*	24%	15%	23%	0.765	0.031	68%	59%	60%	0.114	0.795
Month 18	23%	13%	25%	0.700	0.004	65%	61%	60%	0.281	0.889
Month 24	22%	17%	24%	0.619	0.064	58%	57%	65%	0.158	0.116

* Note: Month 12 results in this table are the same as those presented in the controlled table Month 12 results in the Supportive Tables for the controlled study differ slightly from results in the long-term Supportive Tables due to differences in the datasets for controlled and long-term results. See

Improvements in the PCS score were sustained in the 25 mg etanercept group during the second year of treatment. Compared to the 10 mg group, the 25 mg etanercept group achieved more of these notable improvements in the PCS, which were significant for some parameters at Month 24 ($p = 0.005$ for > 5-unit improvement and 0.020 for >10-unit improvement). No worsening in the MCS scores was observed during Year 2 of the study.

VIII. Safety Results

No safety results are being provided for these long-term protocols in this submission. Safety reviews were required for years 1, 3, and 5, and have been provided for year 3 in a prior submission to FDA.

IX. Financial Disclosure

Clinical trials 16.0009 and 16.0014 were closed prior to implementation of the financial disclosure guidance document, entitled "Financial Disclosure by Clinical Investigators" effective on February 2, 1999. Data collected from these studies were submitted in Immunex's BLA on May 7, 1998 and approved on November 2, 1998. Additionally, fmancia1 disclosure information obtained from Protocols 16.0012 and 16.0023 were submitted in prior supplements to License Number 1132 [February 20,2001 (STN BL 103795/5014) and December 21,2001 (STN BL 103795/5051), respectively].

Forty-five investigators participated in clinical trial 16.0018. Compensation to investigators (as defined in 21CFR§54) for the conduct of study 16.0018 was not dependent on the outcome of the trial. Amgen provided updated financial disclosure information collected from principal investigators and subinvestigators listed on current form FDA1572 for each site participating in study 16.0018. The information is current as of April 2003. Investigators and subinvestigators were asked to completely and accurately disclose or certify information concerning their financial interests which included the following:

- Equity interest in Immunex Corp/Amgen Inc
- Significant payments of other sorts
- Proprietary interest in the tested product
- Payments whose value is contingent upon a positive outcome

No investigator participating in the study has a patent, trademark, copyright, licensing, or other proprietary interest in Enbrel (etanercept). One investigator participating in the study disclosed significant payments of other sorts as defined by the regulation. This investigator received grants, consulting fees and honoraria for speaking totaling between $25,000 - $30,000.

Investigator Name	Site Number	Amount

The investigators listed below disclosed privately purchased holdings of Amgen Inc. common stock in their portfolios that constitute a significant equity interest, estimated to exceed $50,000 based upon the fair market value of Amgen Inc. stock of $58.52 per share on 4/1/03.

Site/Investigator Name	Site Number	Equity Interest

Investigator [redacted] vately purchased and owned stock valued at more than [redacted] t site 478 privately purchased and owned stock valued at more than a [redacted] These two investigators were the largest shareholders participating in studies contributing data to this supplement. Two patients enrolled at site 019 and one patient enrolled at site 478. Therefore, the contributions of these two investigators [a total of 3 patients] with potential for conflict of interest on the overall data is too small to influence the overall results.

X. Overall Summary of Efficacy

The clinical development of etanercept focused on establishing the therapeutic indications of 1) reducing the signs and symptoms, 2) inhibiting the progression of structural damage, and 3) improving health-related quality of life and reducing disability in patients with severely active RA. Physical function and disability were assessed in controlled short-term and open-label long-term studies of etanercept in patients with RA, using the HAQ disability index and the SF-36. The data provided in this supplemental BLA was obtained from controlled short-term and open-label long-term studies of etanercept in patients with severely active RA. Etanercept, administered at a dose of 25 mg twice weekly, was shown to improve physical function in patients with late-stage or early-stage RA, and these improvements were maintained for up to 5 years.

One limitation to the data submitted is that much of the data beyond 6 months is open-label and therefore prone to bias. The RA guidance document calls for evidence of improvement in a disability index, like the HAQ, for 2 to 5 years and no worsening in the SF-36. To avoid the potential for bias, the optimal design for such a study would be a 2-year randomized, double-blind, placebo-controlled trial. Unfortunately it is unrealistic, and possibly unethical, to continue patients on placebo in the face of active disease for 2 years. Therefore, the FDA approach to this submission was to evaluate separately:

1.) Whether there was evidence of drug effect on HAQ in the controlled portions of the trials.
2.) Whether there was evidence for maintenance of benefits out to 2 years in the long-term open-label extension studies.

The HAQ disability index was the primary instrument used to assess improvement in disability in both the early-stage and late-stage patient populations. The SF-36 was added after the study of late-stage RA patients was underway. The results of the SF-36 are submitted as supportive data, and were only available from a small subset of late-stage RA patients. In both RA populations, the mental component summary scores were near normal at baseline and improvements were not different between treatment groups.

In two 6-month, placebo-controlled clinical trials in patients with late-stage RA (Protocols 016.0009 and 016.0014), patients who received 10 mg or 25 mg etanercept, with or without background MTX, had statistically significant improvements in their HAQ disability scores as early as one week and throughout the studies, compared with patients who received placebo or placebo/MTX. Mean improvements in the HAQ at Month 6 were approximately 0.60 units in the 25 mg etanercept groups in two studies of

late-stage RA, compared with 0.03 units in the placebo and 0.18 units in the placebo/MTX groups. At 6 months in the etanercept groups, over two-thirds of patients achieved ≥ 0.25-unit improvements, over half of patients achieved ≥ 0.5-unit improvements, and approximately one quarter achieved ≥ 1.0-unit improvements in their HAQ scores. Significantly smaller percentages of patients achieved these benchmarks in the placebo groups. The results of the SF-36, quite limited by the small number of patients, mimicked those presented for the HAQ scores

In a long-term, open-label extension study of patients with late-stage RA (Protocol 016.0018), improvement in physical function was maintained for the duration of etanercept therapy, for up to 5 years. Throughout the long-term study, over two-thirds of patients achieved a clinically important decrease of ≥ 0.25 units and more than half of patients achieved a decrease of ≥ 0.5 units in the HAQ score.

Assessment of physical function and disability were assessed in controlled and long-term studies of etanercept in patients with early-stage RA, using the HAQ disability index and the SF-36. In an active-controlled 12 month clinical trial of patients with early RA (Protocol 016.0012), patients in all treatment groups had clinically significant improvements in their HAQ scores. At the end of the 12-month active-controlled period, patients in all treatment groups achieved clinically significant improvements from baseline in their HAQ scores. Results with etanercept 25 mg and MTX were similar. However, there was evidence of a dose effect with etanercept in that the 25 mg etanercept group achieved a 0.71-unit mean improvement, higher than the 10 mg group (.55 units).

Patients continued to receive the therapy to which they had been randomly assigned during the second year of the study, and more patients in the 25 mg etanercept group had sustained decrease of ≥ 0.25 units compared with the 10 mg etanercept group.

Both the 10 mg and 25 mg etanercept groups had significantly greater improvements in the physical component summary (PCS) of the SF-36 at 6 months than the placebo group ($p = 0.006$ and 0.022, respectively). In the active-controlled study in early RA patients, the PCS score of the SF-36 was significantly improved in the 25 mg etanercept group, compared with the 10 mg group ($p = 0.005$ at Month 12). These improvements were sustained during the 2- year study. The mental component summary scores were near normal at baseline in both studies, and the improvements were not different among treatment groups. In both placebo-controlled and active-controlled studies, patients who received etanercept had improvements from baseline in the physical component summary of the SF-36, with no worsening in the mental component summary.

Physical function and disability were assessed in controlled short-term and open-label long-term studies of etanercept in patients with RA, using the HAQ disability index and the SF-36. Improvement was observed with etanercept that exceeded a level that is considered clinically meaningful and was maintained for up to 4 years for early-stage and up to 5 years for late-stage active RA. Statistical review by the Agency concurred with this conclusion. Appropriate revisions to the labeling were recommended that incorporated the results from these studies (Appendix 4).

APPENDICES

Appendix 1

HAQ Disability Index

The HAQ disability index is composed of 8 sub domains and 43 questions on the Immunex Case Report. Each question relates to a patient's ability to perform tasks and activities within these 8 subdomains:

1. dressing and grooming,
2. arising,
3. eating,
4. walking,
5. hygiene,
6. reach,
7. grip
8. activity

Responses are self-rated by patients, as described below, on a 4-point Likert scale where:

1 = without any difficulty, 2 = with some difficulty,
3 = with much difficulty, 4 = unable to do.

Patients are also asked to indicate their use of aids and devices or if they need help from another person to perform any of these activities. If the patient indicates that assistance was required to achieve a score of 1 or 2, then the core is reassigned a value of 3. If the patient has completed 1 or more questions on 6 or more of the subdomains, then the disability domain of the HAQ can be computed; otherwise the HAQ score is set to missing for that visit.

The disability index is computed from the mean score of the 8 subdomains. To compute the HAQ score, the scores of the subdomains that had 1 or more completed questions are averaged. This intermediate score will range from 1–4. The final score is computed by subtracting 1 from the intermediate score. Thus, the final HAQ score is on a 0–3 scale with 0 indicating no disability and 3 indicating severe disability. The total score for the HAQ (over time as AUC) will be computed and compared between treatments

Appendix 2

Data Instability

Often the number of patients still in study (not discontinued) at given time-points as shown in the windows of the tables provided in this review did not coincide with the number of patients in the efficacy analyses at that same time-point for several reasons:

(1) Although similar windows were used to define the time points, the date of discontinuation may not have coincided with the date for the efficacy data. Efficacy data in some cases was collected at follow-up after discontinuation and that data was used in analyses.

(2) At the later time-points, patients may have been in the database without known discontinuation status (they may have discontinued and thus no longer have efficacy data at those times-points).

(3) For some 16.0012 time-points, nominal visits were used for the efficacy analyses and these may not coincide exactly with the windows used for these discontinuation status tables.

(4) The HAQ results at the 12-month visit in Protocol 016.0012 do not numerically match the 12-month visit in the long-term supportive tables (to 24 months). However, all statistical comparisons are the same at 12 months, despite these numerical differences.

(5) In the Year 1 dataset originally submitted to FDA for approval (Reference Number 99-0884 on July 15, 1999), 11 patients (n = 1 in MTX, n = 8 in 10 mg, n = 2 in 25 mg) were counted as off-treatment at the 12-month visit because their drug administration records had not yet been received. These patient records were entered later, and therefore, these patients are included as on-treatment at 12 months.

(6) For analyses of the SF-36, one of these 11 patients was included in the original controlled tables. Thus, for SF-36 results, 10 patients do not appear at the 12-month visit in the controlled tables, but they are included in the long-term tables.

Appendix 3

SF-36 Health Survey

Health Related Quality of Life - The SF-36 Health Survey is a comprehensive short-form generic measure of health related quality of life. The survey consists of 36 items, 35 of which are aggregated into eight multi-item scales that measure:

1. ***physical functioning*** **(PF)**
2. ***role physical*** **(RP)**
3. ***bodily pain*** **(BP)**
4. *general health* (GH)
5. *vitality* (VT)
6. *social functioning* (SF)
7. *role emotional* (RE)
8. *mental health* (MH)

These eight scales are hypothesized to form two distinct higher-order clusters, physical and mental health factors, that account for more than 80-85% of the reliable variance in the eight scales in the general US population. Therefore, these two summary measures were constructed from the aggregated scores from all eight scales, and converted into 2 summary scores: a physical component summary (PCS) and a mental component summary (MCS). Three scales **(PF, RP, and BP)** correlate most highly with the physical factor and contribute most to scoring the Physical Component (PCS). Results presented in this submission summarize the two composite scores.

Norm-based scoring was used in all analyses. Norm-based scoring of the SF-36 health profile standardizes each of the 8 scales to have a mean of 50 units and a standard deviation of 10 units in the general U.S. population. The advantage of norm-based scoring is easier interpretation. In norm-based scoring, the general population mean is built into the scoring algorithm. All scores above 50 can be interpreted as above the general population norm, and all scores below 50 can be interpreted as below the general population norm. Furthermore, since the standard deviations for each score are standardized at 10, it is easier to determine how far above or below the norm any score falls (in standard deviation units). Norm-based scoring also allows for direct comparisons of scores across the 8 scales. The original 0-100 scoring of SF-36 scales prohibited this since each scale had a different standard deviation. With norm-based scoring, all SF-36 scales have a standard deviation of 10. In clinical trials of etanercept, patients' responses are summed and transformed to a normalized scale where 0 = worst, 100 = best, 50 = the U.S. norm, and 10 units represent one standard deviation

To convert each of the original 8 subscales to norm-based scores, the general U.S. mean for each subscale is subtracted from the original score and the result is divided by the general U.S. standard deviation. The resulting z-score is then multiplied by 10 and 50 is added, so that the resulting normed score has a mean of 50 and a standard deviation of 10. The summary scores for PCS and MCS are derived from the z-scores of the 8 subscales as follows: each factor coefficient is multiplied by the corresponding z-score

for the sub scale and then summed, to respectively derive the raw PCS and raw MCS score. As described above, the raw PCS and MCS scores are then multiplied by 10 and 50 is added, so that the resulting summary scores have a mean of 50 and a standard deviation of 10.

Appendix 4

Recommended Labeling Revisions

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ)[9]. Additionally, in Study III, the SF-36[10] Health Survey was used to measure the general health-related quality of life. In Studies I and II, patients treated with ENBREL 25 mg twice weekly showed significantly greater improvement from baseline in the HAQ score beginning in month 1, through month 6 in comparison to