CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN 103795/5102

Medical/Statistical Review(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Division of Clinical Trial Design and Analysis
HFM-582

Memorandum

Date: August 21, 2003

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Subject: Clinical Review

Biologic License Application: STN 103795/5102
Product: Etanercept
Indication: Inhibition of Structural Damage in Psoriatic Arthritis
Sponsor: Immunex Corporation

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To: STN 103795/5102

1 INTRODUCTION

1.1 Filing of License Application

On October 21, 2002, Immunex submitted to the Center for Biologics Evaluation and Research a supplemental Biologics License Application (STN 103795/5102) for etanercept for the prevention of structural damage from psoriatic arthritis.

This application contains the final study report of radiographic data in Protocol 16.0030. The primary endpoint of the study was to evaluate the ability (relative to placebo) of etanercept to produce improvement in psoriatic arthritis compared to baseline as measured by ACR response at week 12. The protocol designated a conditional primary endpoint, ——— , of etanercept relative to placebo of radiographic progression of psoriatic arthritis, which was to be assessed if the primary efficacy endpoint was established. Etanercept has demonstrated clinical efficacy in treatment of the signs and symptoms of psoriatic arthritis. Therefore, the conditional primary endpoint has been assessed and submitted to the Agency in this license application.

1.2 Drug Product

Etanercept is a recombinant human tumor necrosis factor p75 receptor Fc fusion protein (TNFR:Fc) produced by recombinant DNA technology in a Chinese hamster ovary mammalian expression system. Etanercept has a molecular weight of ——— is formed by two identical molecules, each consisting of the extracellular portion of p75 tumor necrosis factor receptor (TNFR) fused to the Fc domain of human IgG1. Etanercept acts as a competitive inhibitor of tumor necrosis factor (TNF) binding to the cell surface TNF receptor (TNFR). It, thus, functions as an antagonist of TNF biological activity.

1.3 Rationale and Hypothesis

Psoriatic arthritis is a chronic inflammatory arthritis seen in patients with psoriatic skin lesions that is distinct from other forms of arthritis such as rheumatoid arthritis and osteoarthritis. It is characterized by a variable pattern of joint involvement. Approximately 95% of patients with psoriatic arthritis have involvement of the peripheral joints, of whom the majority have at least 5 involved joints. Some patients have a pauciarticular form of arthritis. Some have exclusively DIP (distal interphalangeal joint) involvement, in contrast to rheumatoid arthritis, which is characterized by PIP (proximal interphalangeal joint) involvement. Approximately 5% have exclusively spinal involvement similar to ankylosing spondylitis, while 20-50% have involvement of both the spine and peripheral joints.

A diagnosis of psoriatic arthritis requires evidence of the skin or nail changes characteristic of psoriasis. In contrast to rheumatoid arthritis, where a female preponderance is seen, men and women are represented roughly equally among patients with psoriatic arthritis. The disease is rare under the age of 13, and the usual age of onset is 30-50 years of age. Psoriatic arthritis is associated with inflammation of the joints and spine, but also of the periosteum, along tendons and at tendon insertion pints, a phenomenon known as ensethopathy. Like rheumatoid arthritis, structural damage to joints can be visualized by radiographic imaging. However, the types of radiographic changes are different. Erosions of the DIPs are seen, which may evolve in severe

cases into terminal whittling of the proximal bone, termed pencil-in-cup deformities. Some studies suggest that the long-term outcome of psoriatic arthritis is better than rheumatoid arthritis. However, joint damage is still significant. A longitudinal study (Gladman DD,1990) showed the proportion of patients with 5 or more damaged joints increased from 19% to 41% over a 5-year time span.

Etanercept was approved for reducing signs and symptoms and inhibiting the progression of structural damage in patients with active early rheumatoid arthritis (≤3 years duration) based on results from an active-controlled study in which patients received methotrexate (MTX) or 10 mg or 25 mg etanercept for 12 months. More recently, two double-blind, placebo-controlled trials led to the approval of etanercept for reducing the signs and symptoms of psoriatic arthritis. An additional objective of this trial was to examine the effect of etanercept on progression of structural damage in psoriatic arthritis.

1.4 Disclosure of Financial Interests and Arrangements of Clinical Investigators

No clinical investigator participating in the study has patent, trademark, copyright, licensing or other proprietary interest in Enbrel.

No clinical investigator disclosed significant payments (in excess of $25, 000) during the period February 2, 1999 through March 1, 2001.

The one clinical investigator listed below disclosed privately purchased holdings of Immunex common stock in his portfolio that constitutes a significant equity interest, estimated to exceed $50,000.

Investigator	Site Number	Date Reported	Number of Shares	Estimated Value (03/01/01)
[redacted]	[redacted]	3/8/00	2400	$78,600.00

1.5 Debarment Certification

Immunex has certified that it has not used the services of any person debarred under Section 306(a) or (b) in connection with this licensing application.

2 CLINICAL STUDY: PROTOCOL 016.0030 X-ray

2.1 Study Title

"Double-blind, Randomized, Placebo-controlled Phase 3 Study of Etanercept (ENBREL) in the Treatment of Psoriatic Arthritis (PsA) and Psoriasis: Radiographic Results"

2.2 Study Objectives

Primary: To establish the clinical efficacy of etanercept with statistical significance at 24 weeks in psoriatic arthritis

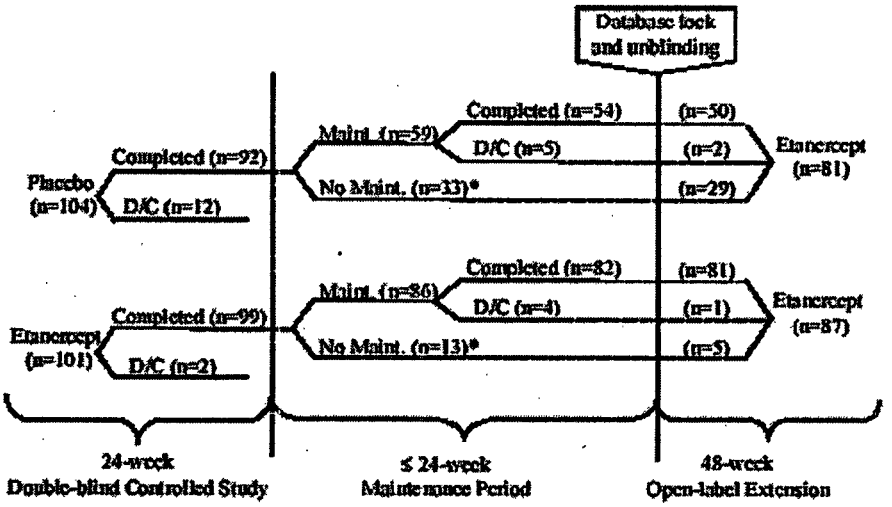
Conditional Radiographic Objectives:

- Primary: to evaluate the ability of etanercept (relative to placebo) to prevent radiographic progression of psoriatic arthritis at 12 months
- Secondary: to evaluate the ability of etanercept to prevent radiographic progression of Psoriatic arthritis at 6 months and at entry into the open-label extension study, and to evaluate changes in psoriatic arthritis-specific radiographic features, including juxta-articular periostitis, and tuft resorption.

2.3 Study Design

This was a double-blind, randomized, placebo-controlled, phase 3 study to evaluate the efficacy and safety of etanercept versus placebo in patients with active Psoriatic arthritis and plaque psoriasis. Patients were stratified by concomitant MTX use. Patients continued to receive study drug, either etanercept or placebo according to their original assignment, in a maintenance period until all patients had discontinued or had completed 24 weeks of blind-labeled study drug and the database was locked. Afterwards, patients were eligible to receive etanercept in a 48-week open-label extension period. The primary radiographic endpoint was measured at week 48 and took place after some of the patients had already entered the open-label extension period. See Figure 1 below.

Figure 1 Study Schema



* Some patients completed study drug in the primary phase of the 24-week controlled study but chose not to continue study drug in the maintenance period. These patients were eligible to enter the open-label extension after database lock and unblinding of the study.

2.3.1 Randomization

The randomization schedule was centrally generated. The randomization/reference number determined study drug and dose assignment. The randomization was stratified by presence or absence of concurrent methotrexate and an equal allocation of patients were to be randomized to each of two treatment groups:

Group 1: 25 mg Etanercept
Group 2: Placebo

Patients were considered randomized at the time that a patient number was assigned. Patients were officially enrolled into the study at the time that they receive the first dose of study drug.

2.3.2 Dosing

Eligible patients were randomized to receive subcutaneous (SC) injections of 25 mg etanercept or placebo administered twice weekly over the 24-week treatment period. Patients could then receive open-label etanercept in a 48-week extension period.

2.3.3 Enrollment Criteria

Inclusion

Men and women aged between 18 and 70 years with active Psoriatic arthritis inadequately responding to therapy. Patients had ≥ 3 swollen joints and ≥ 3 painful/tender joints and at least one of the following subtypes of Psoriatic arthritis: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric peripheral arthritis; or (5) ankylosing spondylitis-like. Patients must also have current, stable plaque psoriasis with a qualifying target lesion. Patients on stable MTX therapy could continue at a stable dose of ≤ 25 mg/week. A 4-week washout period from previous immunomodulatory therapy was required.

Exclusion

Any of the following were grounds for exclusion:

- Previous receipt of etanercept, antibody to TNFα, or experimental metalloproteinase inhibitors (past or current use of minocycline and doxycycline is acceptable)
- Receipt of investigational drugs or biologics within 4 weeks of the screening visit.
- Evidence of skin conditions (e.g. eczema) other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis.
- Receipt of anti-CD4 or diptheria IL-2 fusion protein within the previous 6 months with a subsequent abnormal absolute T cell count.
- PUVA within 4 weeks of study drug initiation. UVB therapy within 2 weeks of study drug initiation.
- Receipt of DMARDs other than methotrexate (e.g., hydroxychloroquine, oral or injectable gold, , cyclophosphamide, cyclosporine, azathioprine, D-penicillamine, or sulfasalazine) or intra-articular corticosteroids within 4 weeks prior to the first dose of study drug.
- Concomitant corticosteroids > 10 mg/day of prednisone (or its equivalent). Corticosteroid dose must be stable for at least 4 weeks prior to screening evaluation.
- Topical steroids, oral retinoids, topical vitamin A or D analog preparations or Anthralin within 14 days of baseline. (Exception - topical therapies are permitted on

scalp, axillae, and groin but must be kept stable throughout trial.)

- Dose of NSAID greater than the maximum recommended dose in the product information. NSAID dose must be stable for at least 4 weeks prior to screening evaluation.
- Pregnant or breast feeding females.
- Significant concurrent medical diseases including:
  - diabetes mellitus requiring insulin
  - uncompensated congestive heart failure
  - myocardial infarction within 12 months of screening visit
  - unstable or stable angina pectoris
  - uncontrolled hypertension
  - severe pulmonary disease (requiring medical or oxygen therapy)
  - history of cancer (other than resected cutaneous basal and squamous cell carcinoma, and in situ cervical cancer) within 5 years of screening visit
  - HIV positive, hepatitis BsAg, or hepatitis C positive
  - rheumatoid arthritis, systemic lupus, scleroderma, polymyositis
  - any condition judged by the subject's physician that would cause this study to be detrimental to the subject.
- Current or history of psychiatric disease that would interfere with ability to comply with the study protocol or give informed consent.
- History of alcohol or drug abuse that would interfere with ability to comply with the study protocol.
- Guttate or pustular psoriasis.
- Active severe infection within 1 month of study drug administration.
- Patients must be off antibiotics for 1 week prior to study drug administration.

2.3.4 Study Drug Administration

Study drug was given twice weekly by subcutaneous injection.

Reconstituted study drug was dispensed to subjects in plastic syringes for administration at home. Subjects were supplied with a diary in which to record the date and time of each study dose as well as adverse events and concomitant medications. Study site staff were to review the diary with the subject at each scheduled clinic visit and transcribe all pertinent information onto the case report form.

2.3.5 Witholding of Drug

No dose reductions of study drug were permitted. Subjects who required a dose reduction were discontinued from study drug. If grade 3 or 4 systemic toxicity occurred that was not alleviated by symptomatic intervention, study drug administration was to be discontinued for no longer than 1 week (two doses of study drug) and resumed when the toxicity has resolved. If grade 3 or 4 toxicity recurs, study drug treatment was to be permanently discontinued.

If the investigator decided to discontinue the study drug due to lack of response, the patient was to receive treatment for psoriatic arthritis as prescribed by the patient's physician. Treatment could not include any investigational drug, DMARD or biologic given under another experimental protocol. Patients were not to receive commercial Enbrel. The patient was to remain in the study for evaluations per the protocol. These patients were allowed to receive open-label etanercept in the open-label extension after this study has been unblinded by Immunex and the database for all subjects has been locked.

2.3.6 Assessments

The schedule of assessments for the blinded portion of the clinical trial (including the 24-week double-blind controlled study and the blinded maintenance portion) is depicted in Table 1 below.

Table 1 Schedule of Evaluations

Assessment	DMARD wash-out Days 0-28	Baseline/ Day 1 Day 1/ Wk 0	Study Drug Administration Wk 4	Wk 8	Wk 12	Wk 24	Maintenance visit	Early term. visit	30 Day Follow-Up 30 D FU
Informed Consent	X								
Medical history	X								
Physical examination[2]	X		X		X	X	X	X	X
Vital Signs	X		X		X	X	X	X	X
Blinded Joint Assessment	X	X*	X		X	X	X	X	X**
Duration of Morning Stiffness	X	X*	X		X	X	X	X	X**
Psoriasis Assessments	X	X*	X		X	X	X	X	X**
Patient Global Assessment/ Physician Global Assessment	X	X*	X		X	X	X	X	X**
HAQ Assessment/ SF-36	X	X*	X		X	X	X	X	X**
Patient assessment of pain	X	X*	X		X	X	X	X	X**
Serum pregnancy test[1]	X								
Hematology Profile	X				X	X	X	X	
Chemistry Profile	X				X	X	X	X	
Urinalysis	X				X	X	X	X	
C-Reactive Protein	X	X*	X		X	X	X	X	X
HIV Screen, Hepatitis BsAg, Hepatitis C	X								
Anti-etanercept/serum bank	X					X			X
X-rays Hands and Wrists		X				X		X[3]	X**
Psoriasis Photograph[3]		X			X	X			
CXR	X								
Serum sample for pneumococcal antigens[4]			X	X					
Pneumococcal vaccine administered[4]			X						

1 If female of child-bearing age or 5 years post-menopausal.
2 Detailed physical at screening; focused physical at other timepoints
3 In subset of patients only
4 Vaccine administered after lab samples collected
* Waived if first dose within 7 days of screening evaluation
** Waived if evaluations were done at EOT visit

Hand and wrist radiographs were taken on study day 1 of double blind treatment (baseline), at week 24, at early termination or at the time that the database was locked, and at 30-day follow-up for the double blind study.

Assessments for the open-label extension (not shown above) included radiographs of the hands and wrists taken at the following timepoints

- At baseline, prior to first dose of open-label treatment;
- At one year from start of initial blinded study drug treatment;
- At 48 weeks from start of open-label etanercept treatment and
- At early discontinuation from study, if > 1 month since last x-ray.

2.3.7 Radiographic Endpoints

Primary Radiographic Endpoint

A comparison of the proportions of patients in the etanercept and placebo groups for:

- The rate of radiographic disease progression (Total Sharp Score, TSS) over 12 months of treatment compared to baseline, using the annualized rate of change. If the interreader and intra-reader correlation of DIP joints was ≥0.8, DIP joints were to be included in the primary analysis.

The primary radiographic endpoint was conditional. The decision to evaluate this was to be based on the outcome of the primary clinical endpoint of the protocol, a comparison of the proportions of patients who achieved an ACR 20 response. The clinical results affirmed that etanercept provides statistically significant improvement in the signs and symptoms of Psoriatic arthritis and, therefore, the radiographic endpoint was evaluated.

Secondary Radiographic Endpoints

A comparison of the proportions of patients in the etanercept and placebo groups for:

- The rate of radiographic disease progression (TSS) from baseline to 6 months.
- The rate of radiographic disease progression (TSS) from baseline to entry into the open-label extension.
- The rate of erosion and JSN scores, viewed independently, from baseline to 6 and 12 months.
- Changes in juxta-articular periostitis, shaft periostitis, and tuft resorption from baseline to 6 and 12 months.

2.3.8 Protocol Amendments

There were four amendments to the original protocol. Amendment 4 (April 15, 2002) made several clarifications to the protocol for scoring the radiographic images. This amendment defined the primary radiographic endpoint as annualized change from baseline to 12 months.

It provided for calculations of correlation between 2 readings of 3 images (baseline, 6 month, and 12-month) for each patient and it included distal interphalangeal (DIP) joints in the primary analysis if the inter-reader and intra-reader correlation of DIPs was ≥ 0.8.

Several secondary endpoints were added: change from baseline to 6 months and to the start of open-label treatment; erosion and joint space narrowing scores viewed independently; change in juxta-articular periostitis, shaft periostitis and tuft resporption at 6 and 12 months; and independent enumeration of presence of pencil and cup deformity, gross osteolysis, joint space widening, ankylosing and joint replacement.

2.3.9 Image Scoring

Two readers selected from a pool of four readers participating in the study scored the set of films for a patient using a modified Sharp method (Appendix 1: Modified Sharp Method). The average of the two scores were used in analysis. The images for a patient were displayed in random time order. A maximum of four images were displayed including images taken at baseline, 6 months, start of open-label, and at 12 months. If any of these were missing, other films taken could be substituted.

The Sharp method scores erosion and joint space narrowing using ordinal scales. Erosion on a 0 (none) to 5 scale; joint space narrowing on a 0 (none) to 4 scale. Erosion and JSN scores are summed across joints and added to produce the Total Sharp Score (TSS). Presence of pencil and cup deformity, gross osteolysis, joint space widening, ankylosing, and joint replacement were enumerated independently as well.

Additionally, radiographs of the hands and wrists were scored for juxta-articular periostitis, shaft periostitis and tuft resorption. Juxta-articular periostitis was scored on a 0 (none) to 4 scale by the number of quadrants with periostitis in of each of 20 joints in each hand. Shaft periostitis was scored as absent or present in the thumb and in the proximal and middle phalanges of the fingers. Each of the 10 digits was scored for depth of tuft resorption.

The change at 6 and 12 months were calculated using the baseline film and the film taken closest to 6 and 12 months, respectively. Patients originally randomized to placebo who entered the open-label study may have already received Enbrel for a few months when the 12-month film was taken. The effect of this would have been to decrease any treatment difference. Change in scores for tuft resorption and juxta-articular and shaft periostitis was determined at 6 and 12 months.

2.3.10 Statistical Analyses

2.3.10.1 Radiographic

For the primary analysis, all patients who received study drug were to be included in the analysis of radiographic endpoints. Change scores were adjusted to 6 or 12-month basis using a linear interpolation/extrapolation of the observed change. For example, if the 12-month image was

taken at 11 months, the change score was to be multiplied by the factor 12/11. The observation closest to the specified time point was used.

Change from baseline was analyzed using the van Elteren test, with stratification for MTX use and reader pair. A 2-sided test was used. The test was to be conducted at the 0.05 level if the primary arthritis endpoint was significant at the 0.05 level.

Subsets of patients were to have their data re-read by the original readers and by all readers. Each reader was to score 12 patients twice to provide estimates of intra-reader variability. Baseline and 12-month films were to be used in this analysis. The results were to be analyzed using methods described by Altman (1983) and Bland (1986). Additionally, correlation between two readings of three images (baseline, 6-month, and 12-month) for a patient were to be calculated.

To provide an estimate of inter-reader variability, all four readers scored a subset of 24 subjects. Baseline and 12-month scores were used in this analysis. Intra-Class Correlation (ICC) was calculated as described by Shrout and Fleiss (1979).

2.3.10.2 Missing Data

All patients who were randomized, who received at least one dose of study drug and who had at least one radiograph were to be included in the radiographic analyses.

If only a baseline film was obtained and the patient withdrew from the study due to lack of efficacy, the patient was to be assigned the worst change score at Month 12 for the patient's quartile at baseline.

If only a baseline film was taken and the patient withdrew due to other reasons, the patient was to be assigned the median change score at month 12 for the patient's quartile at baseline.

2.4 Efficacy Results and Patient Population

2.4.1 Patient Disposition

Two-hundred and five patients were enrolled, randomized and treated-104 in the placebo arm and 101 in the etanercept arm. Seventeen (17) sites in the United States participated. The study took place between March 31, 2000 and August 8, 2002.

Table 2 below shows an accounting of patients through the first 6 months of the study.

Table 2 Patient Disposition

Patient Status	Placebo (N = 104) n	Etanercept (N = 101) n
Completed 12 weeks in study	102	100
Completed 12 weeks on study drug	99	100
Discontinued study drug due to:		
Lack of efficacy (LOE)	2	0
Lost to follow-up	1	1
Patient refusal	2	0
Completed 24 weeks in study	92	99
Completed 24 weeks on study drug	72	93
Discontinued study drug due to:		
Death	1	0
Adverse event	1	1
Lack of efficacy (LOE)	23	5
Lost to follow-up	3	1
Patient refusal	4	1

At least 95% of subjects who enrolled in each of the study arms continued in the study taking study drug until the time of assessment of the primary endpoint at 12 weeks. One subject discontinued study drug before 12 weeks in the etanercept arm, compared to 5 in the placebo arm. The difference was due to a higher number discontinuing due to lack of efficacy (2 in the placebo arm vs. 0 in the etanercept arm) and patient refusal (also 2 in the placebo arm vs. 0 in the etanercept arm).

A higher proportion of subjects continued 24 weeks of blinded study drug in the etanercept arm compared to placebo (98% vs. 88%). The main reasons for the higher discontinuation rate in the placebo arm were lack of efficacy, 23 in the placebo arm vs. 5 with etanercept, and patient refusal, 4 patients in the placebo arm vs. 1 in the etanercept arm. One patient in each arm dropped out due to adverse event.

Duration of exposure to study drug and study completion status including both the initial controlled portion of the study and the open-label extension is shown in Table 3 below.

Table 3 Duration of Exposure and Study Completion Status

	Controlled Portion plus Maintenance		Open-label Extension	
	Placebo (n = 104)	Etanercept (n = 101)	Placebo/ etanercept (n = 81)	Etanercept (n = 87)
Mean (median) duration of exposure (days)	208 (252)	293 (319)	192 (166)	184 (166)
Number (%) patients who completed	87 (84)	95 (94)	76 (94)	81 (93)
Number patients discontinued for:				
Death	1	0	0	0
Adverse event	2	1	0	2
Lack of efficacy	2	0	2	1
Patient refusal	5	2	0	1
Lost to follow-up	5	2	3	2
Protocol violation	1	0	0	0
Other	1	1	0	0

Overall, 84% of placebo patients completed the controlled portion of the clinical trial vs. 94% of the etanercept-treated patients. The most common reasons for study discontinuation in both treatment arms were patient refusal and loss to follow-up, each with a higher number in placebo than in etanercept. Two patients discontinued for lack of efficacy in the placebo arm vs. none in the etanercept arm. During the clinical trial one death occurred in the placebo group.

2.4.2 Study Drug Exposure and Patients with Radiographic Data

The blinded portion of the study was of 24 weeks duration (and could be up to 48 weeks in some patients depending on the length of the maintenance portion) after which patients could enter the open-label extension of an additional 48 weeks. The radiographic endpoint took place at 48 weeks after some of the patients had already entered the open-label extension. Exposure to etanercept by treatment group at the time of the year one radiographic assessment is addressed in Table 4 below.

Table 4 Exposure to Etanercept by Treatment Group: Year 1 Cut-off

Days on Enbrel	**Placebo (N=104)**	**Etanercept (N=101)**
Mean (SE)	27.6 (2.7)	331.6 (7.7)
Std Dev	27.6	76.9
Median	23.0	365.0
Min - Max	0.0 - 93.0	71.0 - 365.0

Note: The analysis included 14 patients in the etanercept arm (of the blinded portion) and 23 patients in the placebo arm who did not enter the open label extension. It is therefore, based on all 205 patients who received study drug (either etanercept or placebo)

Among all 205 patients, exposure to etanercept was 332 days for the etanercept group and 28 days in the placebo group at the time of the one-year assessment.

Reviewer's comment: The mean period of exposure to etanercept in the placebo group prior to the time of the radiographic assessment was not deemed to have an effect on the overall outcome of the radiographic results. Any potential effect of the limited exposure to etanercept by the placebo group would tend to reduce the differences seen between treatment groups.

The proportions of patients for whom there are postbaseline radiographic data at month 6 and month 12 is depicted by Table 5 below.

Table 5 Number of Patients with Available Radiographic Data

	Placebo (n = 104)	Etanercept (n = 101)
Number (%) of patients with:	n (%)	n (%)
Baseline x-ray	104 (100)	101 (100)
Number of patients entering the open-label extension	81	87
X-ray at any time post-baseline	97 (93)	99 (98)
X-ray for Month 6 evaluation		
x-rays taken at 6 months*	88 (85)	96 (95)
x-rays extrapolated/interpolated	9 (8)	3 (3)
X-ray for Month 12 evaluation		
x-rays taken at 12 months*	81 (78)	84 (83)
x-rays extrapolated/interpolated	16 (15)	15 (15)

*Time point +/- 30 days.

All 205 patients had baseline films and 196 patients had at least one post-baseline film. Two patients in the etanercept group and 7 patients in the placebo group had no post-baseline films. The analyses of the radiographic results includes the modified ITT population that includes all 205 patients who received study drug.

2.4.3 Patient Demographics

Baseline demographics are shown in Table 6.

Table 6 Baseline Demographics and Disease History

Characteristic	Placebo (n = 104)	Etanercept (n = 101)
Mean age in years	47.3	47.6
(range)	(21 – 73)	(18 – 76)
Male (n [%])	47 (45)	58 (57)
Race (n [%]):		
Caucasian	95 (91)	91 (90)
Hispanic	5 (5)	6 (6)
Black	2 (2)	3 (3)
Other	2 (2)	1 (1)
Mean weight (kg)	88.4	91.5
Duration of Psoriatic arthritis in years (mean)	9.2	9.0
Duration of psoriasis in years (mean)	19.7	18.3
Mean psoriasis BSA (%)	10.2	10.9
(range)	(1.0 – 90.0)	(0.5 – 80.0)
Evaluable for PASI results (n [%])	62 (60)	66 (65)
No. of prior DMARDs (mean)	1.6	1.7
Concomitant therapy at baseline (n [%]):		
Corticosteroids	11 (11)	15 (15)
NSAIDs	81 (78)	88 (87)
Methotrexate	46 (44)	44 (44)
Subtypes of psoriatic arthritis (n [%]): *		
DIP joints of hand and feet	52 (50)	52 (51)
Arthritis mutilans	2 (2)	1 (1)
Polyarticular arthritis	86 (83)	87 (86)
Asymmetric peripheral arthritis	40 (38)	41 (41)
Ankylosing spondylitis-like	4 (4)	3 (3)

* Some patients were noted to have more than one subtype of Psoriatic arthritis.

Among the 205 patients who participated, the mean age was 47 years. The proportion of male patients in the etanercept treatment arm (57%) was higher than in the placebo arm (45%). The duration of psoriatic arthritis was 9 years in both placebo and treatment arms. The racial distribution, primarily Caucasian, is reflective of the general US population with psoriatic arthritis. The most common concomitant therapy at baseline were NSAIDS followed by methotrexate. Approximately 84% of patients were classified as having polyarticular arthritis followed by DIP involvement of the hands and feet (50%) and asymmetric peripheral arthritis (40%). These characteristics are representative of the US population with psoriatic arthritis. Overall, the two treatment groups were well balanced in terms of demographics and disease history.

2.4.4 Baseline Disease Severity

Table 7 shows the baseline psoriatic arthritis activity measures.

Table 7 Mean (Median) Baseline Psoriatic Arthritis Activity Measures

	Placebo (n = 104)	Etanercept (n = 101)
Status	mean (median)	mean (median)
Tender joint count [a]	22.1 (17.0)	20.4 (18.0)
Tender joint score [b]	31.1 (21.0)	27.5 (22.0)
Swollen joint count [c]	15.3 (12.5)	15.9 (13.0)
Swollen joint score [d]	20.6 (14.5)	22.5 (15.0)
Physician global assessment [e]	2.9 (3.0)	2.9 (3.0)
Patient global assessment [e]	3.0 (3.0)	3.0 (3.0)
Morning stiffness (minutes)	126.8 (60)	118.9 (60)
Pain assessment [e]	3.0 (3.0)	3.0 (3.0)
Disability index (HAQ) f	1.1 (1.0)	1.1 (1.1)
CRP [g]	1.7 (1.1)	2.2 (1.6)

a Scale 0 – 78.
b Sum of 78 joint pain/tenderness scores measured on a 4-point scale.
c Scale 0 – 76.
d Sum of 76 joint swelling scores measured on a 4-point scale.
e 0 = best, 5 = worst (Likert scale).
f 0 = best, 3 = worst.
g Normal range: 0 – 0.79 mg/dL.

The two treatment groups are well-balanced in terms of psoriatic arthritis activity measures, including tender joint count and score, swollen joint count and score, physician global assessment, patient global assessment, morning stiffness and CRP. These measures indicate the population had substantial disease activity at baseline.

The baseline radiographic features are shown in Table 8.

Table 8 Baseline Radiographic Features

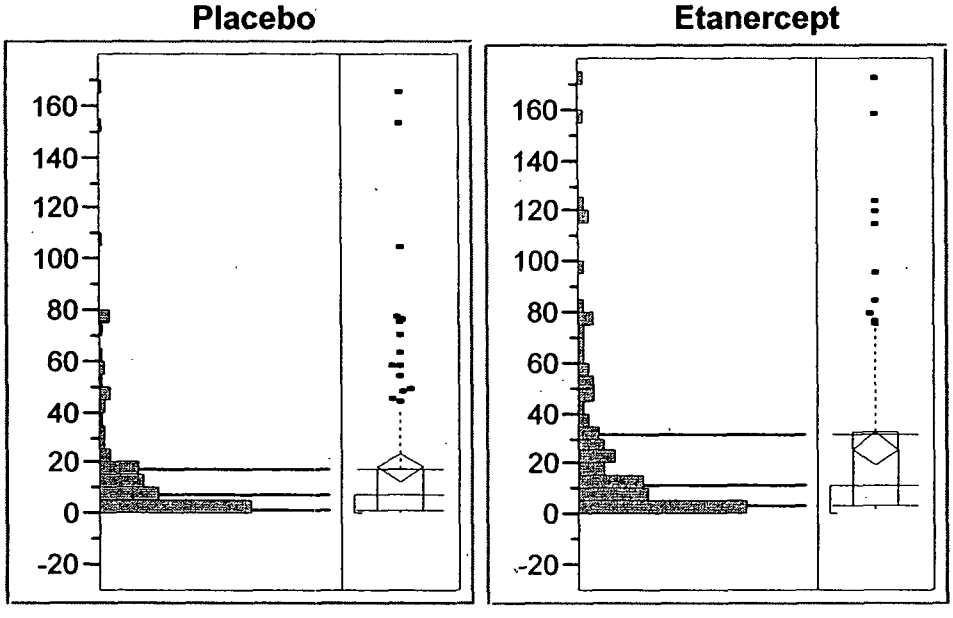
	Placebo (n = 104)	Etanercept (n = 101)
Total Sharp score (median)*	7.5	11.5
range	0 – 165	0 – 172
Erosion score (median)*	3.25	5.5
range	0 – 92.5	0 – 97.0
Joint space narrowing score (median)	4.2	6.0
range	(0 – 72.5)	(0 – 94.5)
Psoriatic arthritis features (n [%])		
Joint space widening	12 (12)	25 (25)
Ankylosis	13 (13)	23 (23)
Pencil-and-cup deformity	3 (3)	11 (11)
Gross osteolysis	6 (6)	17 (17)
Shaft periostitis	29 (28)	43 (43)
Justa-articular periostitis	47 (45)	59 (58)
Phalangeal tuft resorption	39 (38)	44 (44)

* Including DIP joints.

The median TSS was 7.5 in the placebo group and 11.5 in the etanercept group. The median erosion score and JSN score were both higher in the etanercept group than the placebo group (see Table 8). In addition, the radiographic changes characteristic for psoriatic arthritis, including joint space widening, ankylosis, pencil-and-cup deformity, shaft periostitis, juxta-articular periostitis, and tuft resorption were present in greater numbers in the etanercept group. Therefore, as a whole, the baseline radiographic features were numerically worse in the etanercept group than in placebo.

Figure 2 below shows the distribution of baseline TSS by treatment group.

Figure 2 Baseline Total Sharp Score



Maximum	165
75% quartile	17.9
median	7.5
25% quartile	1.5
minimum	0.0

Maximum	172
75% quartile	32.2
median	11.5
25% quartile	3.5
minimum	0.0

There is a shift towards higher TSS in the etanercept-treated group than placebo at baseline. This is apparent in each of the quartiles examined.

Therefore, although demographics (including duration of disease) and disease activity measures were well balanced at baseline of the controlled portion of the study, patients in the etanercept group had more radiographic disease, compared with the placebo group.

Reviewer's comment: The mean measurements for TSS were 26 for the etanercept and 18 for the placebo. The mean measurements were inflated by outliers in this case. Therefore, the median measurements are preferred.

2.4.5 Primary Radiographic Endpoint

The primary endpoint of the study was the annualized rate of radiographic disease progression as measured by TSS over 12 months of treatment compared to baseline. The study protocol stated that if the inter-reader and intra-reader correlation of DIP joints was ≥0.8, the DIP joints were to be included in the primary analysis. The intra-class correlation (ICC) for inter-reader variability of DIP joints was 0.81 (range 0.81–0.88) for TSS at all time points, and the Pearson correlation

coefficient for intra-reader variability was 0.92 for TSS, pooled across readers and time points. Therefore, DIP joints were included in the primary analysis, the comparison of the annualized rate of progression for TSS at Month 12 (see Table 9).

Table 9 Primary Radiographic Endpoint: Mean Annualized Rate of Progression for Total Sharp Score (TSS) at Month 12

	Placebo (n = 104)	Etanercept (n = 101)	P-value*
Mean change in TSS (SE)	1.00 (0.29)	-0.03 (0.09)	0.0001

* P-values were determined using the van Elteren test with stratification for MTX use and reader pair.

The mean change in TSS at one year was 1 unit in placebo and none in the etanercept group. In this analysis, the 9 patients (2 in the etanercept group and 7 in the placebo group) without post-baseline films were attributed change scores of 0. Therefore, the mean change in the placebo group was not increased by this imputation.

Reviewer's comment: The sponsor proposes to include a table similar to table 9 above in the revised label. However, it is not possible to fully describe the data with only mean values. The statistical test used (van Elteren, a stratified Wilcoxon rank test) tested differences in the distribution as a whole. Moreover, the clinical significance of the difference in mean change in TSS between treatment groups (1 unit) is not known.

When the analysis of covariance is performed and the adjusted means from that model are compared, similar statistical results are achieved (data not shown). These analyses were performed for all n = 205 and the for methotrexate strata.

Table 10 shows an analysis of the primary radiographic endpoint excluding the DIP joints.

Table 10 Primary Radiographic Endpoint, Excluding DIP Joints: Mean Annualized Rates of Progression for Total Sharp Score (TSS) at Month 12

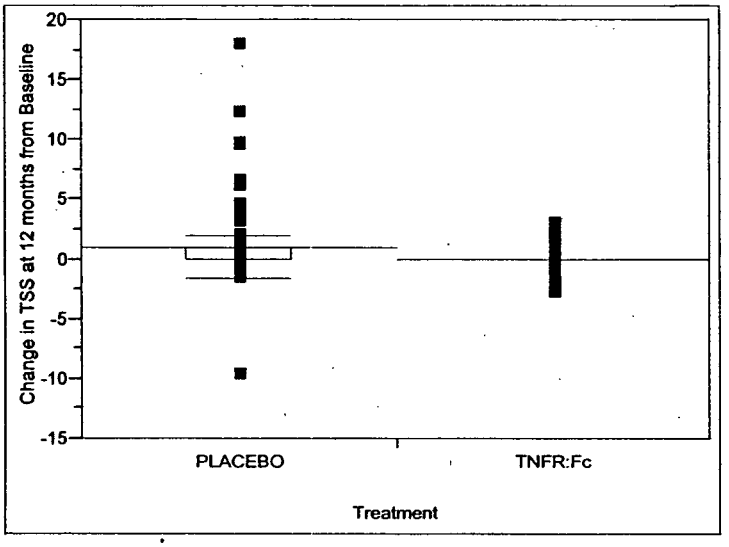
	Placebo (n = 104)	Etanercept (n = 101)	P-value*
Mean change in TSS (SE)	0.64 (0.18)	-0.08 (0.08)	0.0004

* P-values were determined using the van Elteren test with stratification for MTX use and reader pair.

As in the primary analysis, in which DIP joints were included, this analysis also showed a statistically significant effect on radiologic progression. Of note, the sensitivity of the analysis excluding DIP joints would not be expected to be as sensitive for detecting change in the rate of radiologic progression, because DIP joints are frequently affected in psoriatic arthritis patients.

A distribution of the change in TSS at month 12 is shown in Figure 3 below.

Figure 3 Annualized Rate of Progression for Total Sharp Score (TSS) at Month 12: Change in TSS from the Baseline

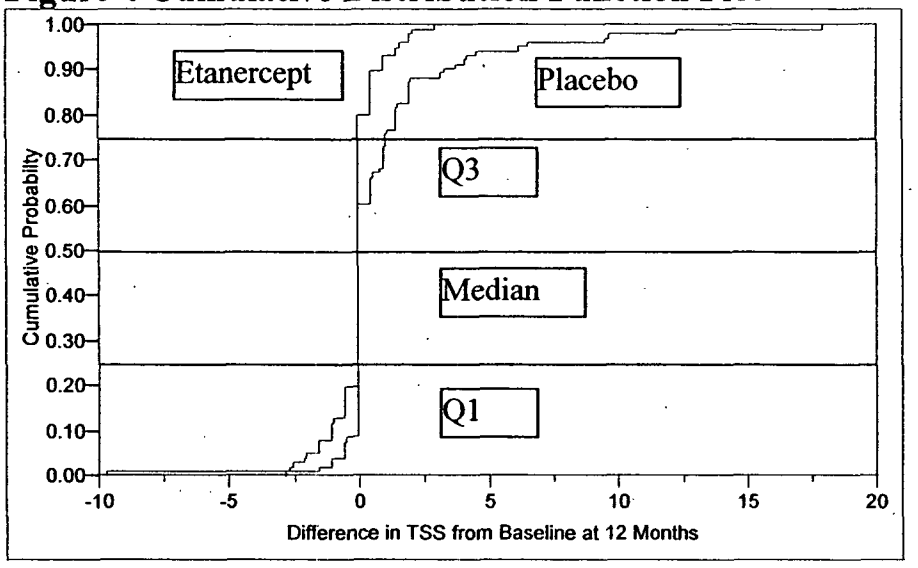


This distribution better describes the treatment effect on radiographic progression by etanercept. Decreases of up to 2.5-3.0 in the TSS were seen in the placebo group suggesting that changes of up to 2.5-3 units represent measurement error, or "noise" (see *reviewer's comment* below). Approximately 10% of patients in the placebo group demonstrated radiographic progression greater than 3 units; whereas, none of the etanercept-treated patients experienced progression of greater than 3 units in TSS.

Reviewer's comment: It would be unexpected to see reversal of the radiographic changes seen at baseline. However, negative changes of up to 2.5-3 were seen in both treatment groups suggesting that changes of this magnitude represent the variability of the assessment method.

These results are also shown in the cumulative distribution plot below.

Figure 4 Cumulative Distribution Function Plot



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
PLACEBO	-9.68466	0	0	0	1.033972	3.542831	17.94581
TNFR:Fc	-2.77305	-1.00179	0	0	0	0.902859	2.945565

Wilcoxon / Kruskal-Wallis Tests (Rank Sums) -- p < 0.0001
Median Test (Number of Points Above Median) -- p = 0.0022
Van der Waerden Test (Normal Quantiles) -- p < 0.0001

From the figure above, the maximum progression seen in any patient was nearly 18 units in a placebo-treated patient. None of the patients in the etanercept group progressed more than 3 units. The median progression was 0 in both treatment groups. Again, a small proportion of patients who showed small negative changes in TSS were deemed to have no change, as the degree of change (< 3 units) was interpreted to be within the error of the scoring system. Therefore, a minority of placebo-treated patients (approximately 10%) had changes of greater than 3 units of progression. Similar changes were not seen in the etanercept treated group. The difference was statistically significant.

Reviewer's comment: The prespecified primary statistical analysis was a comparison of treatment groups by the van Elteren test, a stratified Wilcoxon rank test adjusted for covariates. Although this analysis was successful in demonstrating statistically significant differences in changes in TSS between treatment groups, the clinical significance of these differences were not known. The reports of the two independent experts who reviewed the radiographs supported the use of a 3-unit change in the TSS as a measure of clinically significant radiographic progression. See attached reports of Dr. Williams and Dr. Vasey.

Eighty-seven of the 101 patients in the original etanercept group and 81 of the 104 patients in the placebo group entered the open-label extension (see Table 3). These patients entered the open-label extension prior to completing the 12-month radiographic assessment. This etanercept exposure theoretically could have favorably affected their radiographic outcome at 12 months. Therefore, a secondary endpoint was to evaluate the amount of radiographic progression from baseline to entry (rollover) into the open label portion of the study and annualize this change.

Table 11 Mean (Standard Error) Annualized Rates of Progression at Rollover

	Placebo (n = 104)	Etanercept (n = 101)	P-value*
Mean change in TSS (SE)	1.11 (0.29)	-0.03 (0.10)	0.0020
Mean change in erosions (SE)	0.75 (0.18)	-0.10 (0.08)	0.0002
Mean change in JSN (SE)	0.36 (0.13)	0.07 (0.05)	0.1450

* P-values were determined using the van Elteren test with statification for MTX use and reader pair.

This analysis is consistent with the primary outcome measure at Month 12 (see Table 9).

The responses in the components of the total Sharp score (erosions and joint space narrowing) are shown in the following two tables.

Table 12 Annualized Change from Baseline in Erosion Scores –Including DIPs

Visit		**Placebo (n=104)**	**Etanercept (n=101)**	**p-value ***
6 Months	Mean (SE)	0.33 (0.08)	-0.09 (0.06)	0.0002
Rollover	Mean (SE)	0.75 (0.18)	-0.10 (0.08)	0.0002
1 Year	Mean (SE)	0.66 (0.17)	-0.09 (0.07)	<0.0001

The placebo group had a mean progression in erosion score of 0.66 units compared with none in the etanercept-treated group.

Table 13 Annualized Change from Baseline in Joint Space Narrowing Scores - Including DIPs

Visit		Placebo (n=104)	Etanercept (n=101)	p-value *
6 Months	Mean (SE)	0.20 (0.08)	0.06 (0.05)	0.2033
Rollover	Mean (SE)	0.36 (0.13)	0.07 (0.05)	0.1450
1 Year	Mean (SE)	0.34 (0.13)	0.05 (0.05)	0.0438

* Van Elteren Test

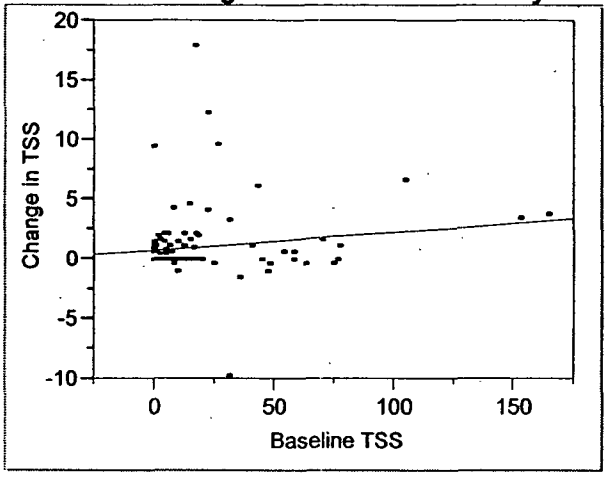
A difference was also seen in the change in joint space narrowing (0.34 in the placebo group vs. 0.5 in the etanercept group). At one year, the differences in change from baseline in both erosion score and joint space narrowing were statistically significant between treatment groups. Thus, both components of the TSS showed benefit with etanercept treatment.

A higher TSS at baseline in the etanercept arm could have potentially affected the rate of radiologic progression. An exploratory analysis was performed to evaluate for any correlation between the rate of radiographic progression and baseline TSS by treatment group. The results are depicted in Figure 5 below.

Figure 5 Radiographic Progression by Baseline TSS

Placebo

Annualized Change in TSS at Month 12 By Baseline TSS



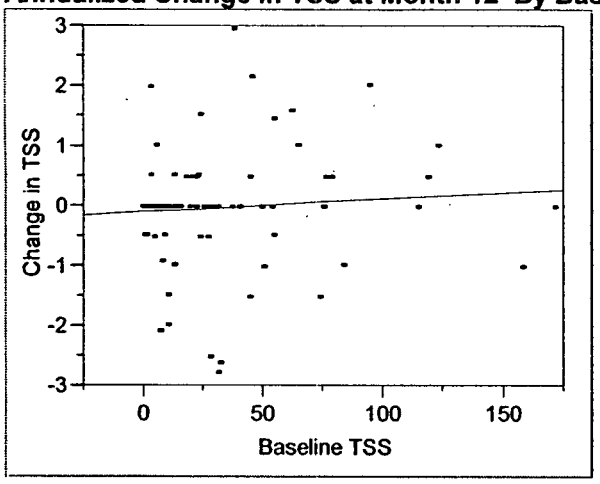
Linear Fit

Change in TSS = 0.7177624 + 0.0153471 Baseline TSS

Summary of Fit

RSquare	0.023237
RSquare Adj	0.013661

Etanercept
Annualized Change in TSS at Month 12 By Baseline TSS



Linear Fit
Change in TSS = -0.089483 + 0.0021969 Baseline TSS

Summary of Fit

RSquare	0.00751
RSquare Adj	-0.00252

This analysis fails to show any meaningful correlation between radiographic progression and baseline TSS in either treatment arm. The Rsquare for the fit was 0.02 for the placebo group and 0.007 for the etanercept group.

2.4.6 Subset Analyses

Exploratory analyses were performed based on baseline disease severity, psoriatic arthritis subtype and demographic variables. The results are shown in the tables that follow.

The median baseline TSS for the study was 10. The following table shows radiographic progression for patients above the median vs. below the median for TSS at baseline.

Table 14 Mean (SE) Annualized Change from Baseline in Total Sharp Scores at 1 Year: ITT Analysis by Baseline Total Sharp Score

Baseline TSS	**Placebo** N=104	**Etanercept** N=101	**p-value**
≤ 10	0.58 (0.19) N=58	-0.03 (0.07) N=46	0.0001
> 10	1.53 (0.59) N=46	-0.03 (0.15) N=55	0.0429

Placebo-treated patients with a baseline TSS higher than the study median showed a greater degree of radiologic progression than those with baseline scores below the study median. The etanercept-treated group showed a mean radiographic progression of 0, in both subsets of baseline TSS (below and above the study median). Other exploratory analyses performed with different cutoffs showed similar results. These included TSS of 7.5 (the median baseline for the placebo group) and TSS of 11 (the median baseline TSS for the etanercept group).

Reviewer's comment: Although these results might suggest that patients with higher baseline TSS score might be more likely to demonstrate radiographic progression over time, this conclusion was not supported by the analysis shown in Figure 5 above.

The change from baseline in mean TSS (including DIPs) for subgroups defined by age, gender, and body weight is shown below.

Table 15 Mean (SE) Change from Baseline in Total Sharp Score at 1 Year: ITT Analysis by Demographic Subgroup

	Placebo	Etanercept
Age		
<65	0.99 (0.30)	-0.04 (0.09)
	N=99	N=93
≥ 65	1.20 (0.88)	0.06 (0.20)
	N=5	N=8
Gender		
Male	0.90 (0.50)	0.02 (0.13)
	N=47	N=58
Female	1.08 (0.32)	-0.10 (0.11)
	N=57	N=43
Weight*		
≤ Study Median	1.40 (0.44)	-0.08 (0.12)
	N=53	N=50
> Study Median	0.59 (0.35)	0.1 (0.13)
	N=51	N=51

* Median body weight in the study was 89 Kg.

Across subgroups, the estimated treatment effect is similar. The number of patients with age ≥ 65 was small. However, even among this small number of patients, there was a clear trend toward reduction in radiographic progression. Changes in total Sharp score between treatment groups revealed evidence of treatment effect in both males and females. Heavier placebo-treated patients had less radiographic progression than their lighter counterparts; however, in treated patients this difference was not seen. Both subgroups of etanercept-treated patients showed practically zero change in TSS over one year.

An exploratory analysis of treatment effect by psoriatic arthritis subtype is shown in Table 16 below.

Table 16 Annualized Change from Baseline in Total Sharp Scores-Including DIPs: –ITT Data at 1 Year by Psoriatic Arthritis Subtype

Type	Placebo	Enbrel
Polyarticular	1.16	-0.05
	(n=86)	(n=87)
DIP involvement	1.07	-0.03
	(n=52)	(n=52)
Asymmetric Peripheral Arthritis	0.67	0.36
	(n=40)	(n=41)
Arthritis Mutilans	3.54	0.0
	(n=2)	(n=1)
Ankylosing Spondylitis-like	-2.42	-1.81
	(n=4)	(n=3)

Polyarticular and DIP involvement subtypes showed differences in progression in favor of the etanercept group that achieved statistical significance. In addition, asymmetric peripheral arthritis subtype showed a trend towards less progression in the etanercept–treated group. The numbers of patients with arthritis mutilans and ankylosing spondylitis subtypes were too small for meaningful analysis.

An analysis of radiographic progression by duration of psoriatic arthritis is shown in Table 17 below. The study median for duration of psoriatic arthritis was 9 years.

Table 17 Change from Baseline in Total Sharp Score at 1 Year- Annualized Change from Baseline Subjects by Duration of Psoriatic Arthritis

		Placebo N=104	**Enbrel N=101**	**p-value ***
≤ Study Median	Mean (SE)	0.89 (0.35)	-0.25 (0.12)	0.0003
		N=54	N=49	
> Study Median	Mean (SE)	1.12 (0.46)	0.17 (0.12)	0.0502
		N=50	N=52	

* Van Elteren test

Treatment effect was seen in both subgroups of patients by duration of psoriatic arthritis.

Concurrent methotrexate usage was a stratification variable in randomization scheme. The analysis in Table 18 below shows the rates of radiographic progression in treatment groups by concomitant methotrexate usage.

Table 18 Mean Annualized Rates of Progression at Month 12, MTX vs non-MTX Concomitant Therapy

	MTX			Non-MTX		
	Placebo (n = 43)	Etanercept (n = 42)	P-value*	Placebo (n = 61)	Etanercept (n = 59)	P-value*
Total Sharp Score	0.83	0.10	0.0482	1.12	-0.13	0.0008
Erosion Score	0.60	-0.01	0.0034	0.71	-0.14	0.0003
JSN	0.23	0.11	0.5450	0.41	0.01	0.0294

* P-values were determined using the van Elteren test, stratified by reader pair.

Treatment effect was seen irrespective of concomitant methotrexate use. However, the difference between treatment groups was greater in the non-methotrexate stratum.

An analysis of those patients achieving zero progression (≤ 0 change) in annualized TSS from baseline to Month 6, Month 12, or rollover showed statistically higher numbers in the etanercept group at all timepoints (see Table 19 below).

Table 19 Zero Progression in Annualized TSS Over Time

	Placebo (n = 104)	Etanercept (n = 101)		Odds Ratio	95% Confidence
≤ 0 change in TSS at:	n (%)	n (%)	P-value*	(OR)†	Interval (CI)†
Month 6	67 (64)	83 (82)	0.0046	2.49	(1.30, 4.77)
Rollover	67 (64)	80 (79)	0.0223	2.04	(1.09, 3.82)
Month 12	63 (61)	81 (80)	0.0027	2.57	(1.36, 4.83)

* P-values were determined using the Cochran-Mantel-Haenszel test with stratification for MTX use and reader pair.
† Mantel-Haenszel estimate of OR with 95% CI

The sponsor compared the radiographic outcomes to the clinical outcomes using ACR-N. The ACR-N was derived from the ACR definition of improvement in RA and was computed as the least of % improvement in swollen joint count, % improvement in tender joint count, and third most % improved of the remaining 5 components of the ACR response criteria.

Table 20 Pearson Correlation Coefficients Between Radiographic and Clinical Data at Month 12

	Correlation coefficient (r)	P-value*
TSS	-0.20892	0.0026
Erosion	-0.22424	0.0012
JSN	-0.15454	0.0269

* P-values determined using the t-test for $\rho = 0$.

ACR-N was negatively correlated with radiographic progression ($p<0.05$), although weakly ($r<0.25$). The weakest correlation was with JSN.

2.4.7 Psoriatic Arthritis-Specific Radiographic Endpoints

Secondary rediographic endpoints included an analyses of psoriatic arthritis-specific radiographic features. These features include joint space widening, ankylosis, pencil-and-cup deformity, shaft periostitis, juxta-articular periostitis, and tuft resorption.

Table 21 Patients with PsA-specific Radiographic Features at Baseline and at Month 12 (Patients with both baseline and follow-up values)

	Placebo		Etanercept	
	Baseline (n = 97)	Month 12 (n = 97)	Baseline (n = 99)	Month 12 (n = 99)
Psoriatic arthritis features*	n (%)	n (%)	n (%)	n (%)
Joint space widening	10 (10)	11 (11)	25 (25)	25 (25)
Ankylosis	12 (12)	14 (14)	22 (22)	22 (22)
Pencil-and-cup deformity	3 (3)	3 (3)	11 (11)	11 (11)
Gross osteolysis	6 (6)	7 (7)	17 (17)	16 (16)
Shaft periostitis	27 (28)	27 (28)	41 (41)	41 (41)
Juxta-articular periostitis	45 (46)	46 (47)	58 (59)	58 (59)
Phalangeal tuft resorption	36 (37)	37 (38)	43 (43)	43 (43)

* Scores shown include DIP joints.

No progression in any of the psoriatic arthritis specific features was noted in the etanercept group. Overall, the changes seen in the placebo group were too small to draw any firm conclusions with regard to psoriatic arthritis-specific radiographic features during this time period.

2.4.8 Concurrent Medication Use

An analysis regarding the concomitant use of disease modifying antirheumatic drugs (DMARDs) during the study, both blinded and open-label portions, is depicted in Table 22.

Table 22 Additional DMARD Use

	Randomization	Actual	Blinded (n=205)	Open Label (n=168)
PBO	MTX (n=43)	N=46	3 patients received new DMARDS (2 enbrel and 1 sulfasalazine)	No patients started other DMARDS (39/46 continued MTX)
	NO MTX (n=61)	N=58	8 patients received new DMARDS (5 MTX, 2 sulfasalazine and 1 enbrel + MTX	4 of 42 patients who entered the open label study started MTX
Enbrel	MTX (n=42)	N=44	No patients started other DMARDS	No patients started other DMARDS (40/42 continued MTX)
	NO MTX (n=59)	N=57	2 patients took additional DMARDS (1 sulfasalazine, 1 MTX)	1 of 47 patients who entered the open label study started MTX

All patients who received new DMARDS during the blinded phase started the indicated DMARD on or after the day of the last dose of study drug in the blinded phase. The number of patients initiating additional DMARD use during the blinded phase was greater in the placebo-treated group (n=11) than in the etanercept group (n=2). The effect (if any) would be to lessen the rate of progression in the placebo group.

2.5 Summary of Efficacy

- There is a statistical difference in the mean rate of radiographic progression between the treatment arms, one point in the total Sharp score at 12 months. However, the mean progression in the placebo arm is driven by a small number of patients (~10%) who experienced larger degrees of radiographic progression. The median radiographic progression in both of the treatment arms was zero with the vast majority of patients in both arms showing no radiographic progression at one year.
- Two independent experts in radiographic changes in psoriatic arthritis supported the use of 3 units of change in TSS as a clinically significant measure of radiographic progression.
- A small number of patients in the placebo group showed a change in 3 units in TSS (up to change in TSS of 18) affecting the mean value in total Sharp score. No patients in the etanercept group showed increases of this magnitude.
- Both components of the TSS (erosions and JSN scores) in those patients who received etanercept showed statistically less progression than placebo-treated patients.
- Statistically significant differences in radiologic progression in favor of etanercept were demonstrated in patients with both polyarticular and DIP predominant subtypes of Psoriatic arthritis. Mean changes in TSS in patients with the asymmetric peripheral

arthritis subtype of psoriatic arthritis showed a trend towards reduction in radiologic progression. The numbers of patients with ankylosing spondylitis and arthritis mutilans were too small for a meaningful analysis.

- Similar benefits were observed among various demographic subsets (age, gender, body weight) and among patients with baseline disease severity and duration of disease both above and below the study median.
- Inhibition of radiographic progression was seen in patients regardless of concomitant methotrexate use.
- The proportions of patients with psoriatic arthritis-specific radiographic features were not significantly changed in either treatment group at 12 months compared to baseline.
- ACR-N showed a weak negative correlation with radiographic progression; patients who had the best clinical responses tended to have the least amount of radiographic progression.

2.6 Safety Results

There were no deaths reported during the maintenance period and the open label periods. The following is a tabulation of the serious events during the maintenance and open label periods.

Table 23 Serious Adverse Events During Maintenance and Open-label Extension

Pt. No.	SAE*	Discontinuation due to AE*
Placebo in maintenance		
0030	Carcinoma (liver metastasis)	Carcinoma (liver metastasis)
0536	Prostate carcinoma	Prostate carcinoma
Etanercept (in maintenance or open label extension)		
0577	Asthma	
0592	Prostate carcinoma	Prostate carcinoma
7008	Pneumonia	
7012	Lung disorder (COPD)	
7018	Coronary artery disorder	
7037	Ischemia cerebral	
7041	Herniated disk	
7048	Vaginal hemorrhage	Liver function abnormality
7063	Kidney calculus	
7510	Angina pectoris	
7519	Pancreatitis	
7525	Lung disorder (COPD)	
7553	Skin carcinoma	
7557	Depression	
7597	Angina pectoris	
7603	Heart failure	

Of the serious adverse events reported, one was classified as infectious (see the narrative below).

Patient no. 7527

The patient was a 56-year-old male with chronic obstructive pulmonary disease (COPD) with bullous emphysema and CLL who was diagnosed with psoriasis and psoriatic arthritis 6 years prior to enrollment. He received blinded study drug (etanercept) in the non-MTX stratum. Concomitant medications included rofecoxib and prednisone. Approximately 11 months from the initiation of etanercept (3 weeks into open label treatment) he was hospitalized for exacerbation of COPD. He received intravenous (IV) levofloxacin for suspected bacterial infection in addition to albuterol, iprotropium, solumedrol, and prednisone; there was no study drug interruption. No pneumonia was noted on chest X ray and oxygenation was 93%. The patient's course was uncomplicated. During the course of his hospitalization, the patient revealed the diagnosis of chronic lymphocytic leukemia (1985). He had not told the investigator at the time of blinded study enrollment. The patient's white blood cell count remained stable over the course of the study. The investigator and sponsor consider the acute exacerbation of COPD to be unrelated to study drug.

One patient a 42-year-old man (patient no. 7037) without known cardiovascular risk factors suffered a transient ischemic attack. The patient received etanercept in MTX stratum of controlled portion. He received last study drug on day 417. He was hospitalized on day 418 for transient ischemic attack. He was treated with IV heparin and oral warfarin and symptoms resolved. The patient withdrew consent and discontinued from open-label extension on day 507. The event was classified as unrelated.

Of the other cardiovascular adverse events reported, all of the patients did have coronary risk factors. See the following narratives.

Patient no. 7018

The patient was a 55-year-old Caucasian female who was diagnosed with psoriasis and with psoriatic arthritis. Additional medical history included hypertension, hypothyroidism (Grave's disease with radioactive iodine therapy and hemithyroidectomy), gastroesophageal reflux disease, methotrexate-induced liver disease (Grade 1), degenerative joint disease with cervical and lumbar spondylosis, osteopenia, and fibromyalgia.

The patient received placebo in MTX stratum of controlled portion. Hospitalized on D184 of open-label extension for unstable angina and underwent coronary artery bypassgraft. Completed open-label. The adverse event was classified as unrelated by the investigator and the sponsor concurs.

Patient no. 7510

The patient was a 63-year-old female whose medical history included hypertension and fibromyalgia. She received etanercept in non- MTX stratum of controlled portion. She was hospitalized on day 419 for unstable angina, which resolved with additional antianginal and diuretic medications. She completed the open label extension. The adverse event was classified as unrelated by the investigator and the sponsor concurs.

Patient no. 7597

The patient was a 50-year-old male whose medical history included hypertension, coronary artery disease, cardiac arrhythmia, diabetes mellitus, hyperlipidemia, nephrolithiasis, and depression. He received etanercept in non-MTX stratum of controlled portion. He was hospitalized on day 375 for unstable angina, which resolved with glyceryl trinitrate. The patient was withdrawn from open-label extension due to noncompliance. The adverse event was classified as unrelated by the investigator and the sponsor concurs.

Patient no. 7603

The patient was a 58-year-old male whose medical history included coronary artery disease, congestive heart failure, cardiac arrhythmia, hyperuricemia, obesity, and depression. The patient received placebo in non-MTX stratum of controlled portion. He was hospitalized on day 37 of open-label extension for CHF decompensation with newly diagnosed left bundle branch block. He completed open-label study. The adverse event was classified as unrelated by the investigator and the sponsor concurs.

Five patients discontinued study drug for safety-related reasons during the maintenance and open label extension periods of the study.

Table 24 Safety-related Discontinuations of Study Drug During Maintenance or Open-label

Patient No.	Sex/ Age	Day of D/C	Grade	COSTART Term	Comments/Relationship to Study Drug
Placebo (maintenance)					
0030	F/64	303	3	Carcinoma (with liver metastasis)	1991: salpingo-oophorectomy for fallopian tube cancer 1993: hysterectomy for cervical cancer Completed controlled portion (MTX stratum) Diagnosis: metastatic adenocarcinoma fallopian tube origin Unrelated
0536	M/49	312	3	Prostate carcinoma	Completed controlled portion (non-MTX stratum). Wk 33: Prostate biopsy: moderately differentiated adenocarcinoma. Wk 43: received radiation implant Unrelated
Etanercept (maintenance)					
0592	M/76	271	3	Prostate carcinoma	History: prostatectomy for enlarged prostate Completed controlled portion (non-MTX stratum). Discontinued D271 for prostate carcinoma. Unrelated
Open-label extension					
7048	F/46	449	2	Liver function abnormality	Patient in MTX stratum /controlled portion MTX dose reduced during maintenance and discontinued during open-label extension due to elevated LFTs. D400: Hospitalized for vaginal bleeding hysterectomy (found: benign ovarian cyst, uterine fibroids,cervicitis) Discontinued on D449 due to elevated LFTs. Unrelated.
7619	M/63	338	1	Paresthesia	Patient in non-MTX stratum D141 of controlled portion: numbness and splinter hemorrhages of fingers Diminished right biceps deep tendon reflex noted at rollover to open-label. Neurologic and laboratory evaluations: (+ACL antibody, factor V Leiden heterozygosity, and prolonged PTT) consistent with vasculitis/vasculopathy. Unrelated.

The adverse events leading to discontinuation of study drug were classified by the investigator as unrelated to study drug in each case. Other than Patient No. 7048 discussed above, no patients discontinued due to abnormal laboratory values.

Patient no. 7619

The patient was a 63-year-old Caucasian male who was diagnosed with psoriasis in 1960 and with psoriatic arthritis in 1968 (polyarticular without DIP involvement). Additional medical history included hyperlipidemia stress/depression. Treatment history included methotrexate (MTX), azathioprine, parenteral gold, NSAIDs, and oral corticosteroids. At the time of enrollment, the patient remained on celecoxib and prednisone; other ongoing medications included atorvastatin, sertraline, calcium supplements, and vitamin E.

The patient received blinded study drug (etanercept) in the non-MTX stratum for 9 months beginning on [redacted]. On Week 21, the patient experienced the onset of numbness of the fingers (Grade 1, ongoing). On Week 36, the patient manifested splinter hemorrhages involving all fingers (Grade 1), for which he received nifedipine and warfarin was added. Anti-cardiolipin antibody was positive.

Screening physical examination for the open label period was notable for diminishment of the right biceps deep tendon reflex. Subsequently, the patient was noted to have factor V Leiden heterozygosity and prolonged PTT. On [redacted], the study drug was permanently discontinued due to parasthesias of the fingers (Grade 1). On [redacted], the patient had a neurologic evaluation, including results of MRI, and the neurologist concluded the symptoms were most consistent with vasculitis/vasculopathy.

On [redacted], the patient developed pain in the right mid-foot with cord-like changes and was diagnosed with superficial phlebitis. On [redacted], 4 months after study drug discontinuation, the patient was hospitalized for management of deep vein thrombosis. He underwent placement of a vena cava filter; warfarin was re-instituted. On [redacted] the patient was discharged, without reported complication.

The investigator considered the parasthesias of the fingers to be unrelated to the study drug. Immunex concurs.

Reviewer's comment:
Patient 7619 possibly had a drug- induced vasculitis. Autoimmunity has been associated with anti-TNF agents. Vasculitis and deep vein thrombosis are included in the labeling under Adverse Reactions. If other reports of vasculitis associated with antiphospholipid antibodies are seen, consideration should be given to adding appropriate information to the label.

A review of all adverse events per patient year by study period did not show any new patterns with regard to safety events in the open-label period compared with the blinded period.

2.7 Summary of Safety

This supplement contains safety data aquired during the maintenance and open-label portion of the protocol. The safety data from the controlled portion of the study has already been reported to the FDA.

No deaths were reported during the maintenance and open-label portions of the study. During the maintenace period, 2 patients in the etanercept group and 2 patients in the placebo group experienced serious adverse events; 14 additional serious adverse events were reported in the open-label extension. Rates per patient-year of adverse events and infections were comparable to or less than those observed in the controlled portion of the study.

Of the serious adverse events that were cardiovascular in nature, most occurred patients who had at least one pre-existing risk factor or a previous diagnosis of coronary disease. One patient (age 42) without known risk factors suffered a transient ischemic attack and fully recovered with therapy. Cerebral ischemia is contained within the current label under Other Adverse Reactions.

One patient (7619) possibly had a drug-induced vasculitis. Autoimmunity has been associated with anti-TNF agents. Vasculitis and deep vein thrombosis are included in the labeling under Adverse Reactions/ Adverse Reaction Information from Spontaneous Reports. In addition, the label states under Adverse Reactions/ Autoantibodies that the proportion of patients treated with etanercept who developed anticardiolipin antibodies was increased compared to placebo-treated patients. If other reports of vasculitis associated with antiphospholipid antibodies are seen, consideration should be given to adding appropriate information to the label.

3 CONCLUSIONS AND RECOMMENDATIONS

While etanercept appeared to reduce the rate of radiographic progression, most patients in both groups had small amounts of progression or none. The number of patients in the control group with large degrees of radiographic progression is small (approximately 10%). No patients in the etanercept arm experienced large degrees of progression (>3 units in TSS).

1. Based upon the data, the sponsor should be given an indication for the inhibition of radiographic progression in psoriatic arthritis.

2. The mean data do not demonstrate the fact that all of the clinical benefit took place in a small proportion of patients. Thus, in the representation of the study's findings, the mean data should not be used because this would be misleading. Instead, the data should describe the fact that the differences are based upon changes seen in a minority of patients in the placebo group that were not seen in etanercept-treated patients.

3. With regard to adverse events, no changes to the label are indicated at this time. However, one patient was noted to have a vasculitis associated with antiphospholipid antibodies. If other reports of vasculitis associated with antiphospholipid antibodies are seen, consideration should be given to adding appropriate information to the label.

Appendix 1: Modified Sharp Method According to the Sponsor's Hand Radiography Manual

The original Sharp Method scored 27 joints of each hand-wrist for erosions and joint space narrowing (JSN) (Sharp JT 1971).

In 1985, the Sharp method was revised to score 17 joints of each hand-wrist for erosions and 18 joints for JSN.

For the evaluation of psoriatic arthritis in this study, the method has been further modified such that 21 joints of each hand-wrist were scored for erosions and 20 joints of each hand-wrist were scored for joint space narrowing. The DIPs have been added to reflect the degree of their involvement in psoriatic arthritis.

Scoring Methodology:
The original Sharp score for erosions was a scale from 0 to 5 based on the number of erosions in each joint.

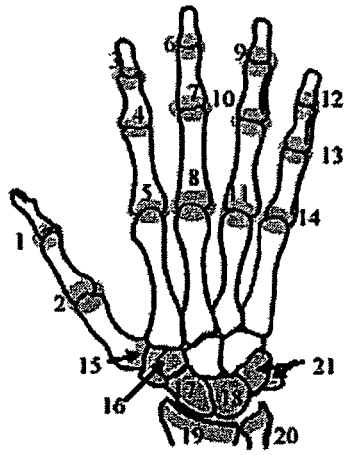
The scale for scoring erosions has been modified for this study and is now a scale from 0 to 7 and includes pencil cup osteolysis and gross osteolysis. Also, instead of counting only discrete erosions as described in the original Sharp method, the use of the scale has been modified such that a one integer increase or decrease in the score for each joint was allowed if there has been a change in the number of erosions or $\geq$ 20% change in the area eroded.

The 0-7 scale for erosions was as follows (page 7 of the sponsor's hand radiography manual):

- 0 - no erosions
- 1 - one discreet erosion or involvement of less than 21% of the joint area by erosion
- 2 - two discreet erosions or involvement of 21 through 40% of the joint
- 3 - three discreet erosions or involvement of 41 through 60% of the joint
- 4 - four discreet erosions or involvement of 61 through 80% of the joint
- 5 - extensive destruction involving more than 80%
- 6 - Pencil Cup Osteolysis
- 7 - Gross Osteolysis
- C - surgery/joint replacement
- D - subluxation/superimposition
- E - OA or other arthritis
- F - radiographically inadequate

The following depicts the joints for erosions and osteolysis scoring from page 9 of the radiographic manual.

The Joints for Erosion and Osteolysis Scoring



1	1st IP	12	4th DIP
2	1st MCP	13	5th PIP
3	2nd DIP	14	5th MCP
4	2nd PIP	15	MC1
5	2nd MCP	16	Multangular
6	3rdDIP	17	Navicular
7	3rd PIP	18	Lunate
8	3rd MCP	19	Radius
9	4th DIP	20	Ulna
10	4th PIP	21	Triq/Pis
11	4th MCP		

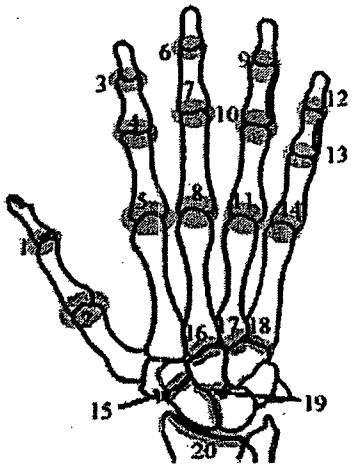
The original Sharp score for JSN was on a scale from 0 - 4. The scale for JSN has also been modified for this study and is now a scale from 0 to 5 and includes joint space widening.

The scale for scoring joint space narrowing was as follows (page 12 manual):

- 0 - no narrowing
- 1 - asymmetrical and or minimal narrowing
- 2 - definite narrowing with loss of up to 50% of the normal space
- 3 - definite narrowing with loss of 51 to 99% of the normal space
- 4 - absence of a joint space, presumptive evidence of ankylosis
- 5 – Wide
- C - surgery/joint replacement
- D - subluxation/superimposition
- E - OA or other arthritis
- F - radiographically inadequate

The following depicts the joints for scoring of joint space narrowing from page 14 of the sponsor's radiographic manual.

The Joints for JSN Scoring



1	1st IP	12	5th DIP
2	1st MCP	13	5th PIP
3	2nd DIP	14	5th MCP
4	2nd PIP	15	MNA
5	2nd MCP	16	CMC 3
6	3rd DIP	17	CMC 4
7	3rd PIP	18	CMC 5
8	3rd MCP	19	CAPN
9	4th DIP	20	Radius
10	4th PIP		
11	4th MCP		

Appendix 2: American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis

Required ≥20% improvement in tender joint count and ≥20% improvement in swollen joint count

+

≥20% improvement in 3 of following 5: Subject pain assessment, Subject global assessment, Physician global assessment, Subject self-assessed disability, Acute-phase reactant (ESR or CRP)

Disease activity measure	**Method of Assessment**
1. Tender joint count	ACR tender joint count modified, an assessment of 78 joints. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The single tender-versus-nontender dichotomy.
2. Swollen joint count	ACR swollen joint count modified, an assessment of 76 joints. Joints are classified as either swollen or not swollen.
3. Subject assessment of pain	A horizontal visual analog scale (usually 10 cm) or Likert scale assessment of subject's current level of pain.
4. Subject's global assessment	The subject's overall assessment of how the arthritis is doing. An anchored horizontal visual analog scale (usually 10 cm) or Likert scale response is acceptable.
5. Physician's global assessment	A horizontal visual analog scale (usually 10 cm) or Likert scale measure of disease activity of the physician's assessment of the subject's current disease status.
6. Subject's assessment of physical function	Any subject self-assessment instrument which has been validated, has reliability and has been proven in RA trials to be sensitive to change, and which measures physical function in RA subjects is acceptable. Instruments which have been demonstrated to be sensitive in RA trials include the AIMS, the HAQ, the Quality (or Index) of Well Being, the MHIQ, and the MACTAR
7. Acute-phase reactant value	A Westergreen erythrocyte sedimentation rate or a Creactive protein level

* Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995; 6:727-735

Appendix 3: Intrareader and Intrareader Correlations

Reader Pairs

The 4 readers were assigned to read x-rays as 6 possible reader pairs. One pair, blinded to study therapy and chronological order of the images, scored each patient's radiographs. The average of the 2 scores was used in subsequent analyses. Prior to the films being read, the study had been unblinded and analyzed for safety and for efficacy of the primary clinical outcome variable. In order to maintain the blind on the films to the readers and the Sponsor, a dummy patient number was assigned by the clinical research organization responsible for the radiographic data [redacted]. The dummy patient numbers were not unblinded until the radiographic data were locked.

In order to preserve the balance of reader pairs across treatment groups and methotrexate use strata, each reader pair was assigned to a patient's film based on a patient list (stratified by treatment and methotrexate use) provided to [redacted] by the Sponsor. The first pair of readers was assigned the first patient on the list; the second reader pair was assigned the second patient, etc.; after the sixth patient had been assigned, another round of assignments was made until all patients had been assigned a reader pair.

To measure inter- and intra-reader variability, the radiographs from 24 patients that had been previously read by one pair of readers were read again by all 4 readers. In order to preserve balance across baseline disease status and reader pair, 4 patients were randomly selected from those read by each pair (2 with baseline TSS above the overall median, and 2 with baseline TSS below the overall median). Inter-reader correlation was measured using the data set of all 24 patients that were scored by each reader. It was also possible to measure intra-reader variation since each reader scored 12 patients twice.

Inter-reader correlations were analyzed using methods described by Shrout (1979) for the Intra-class Correlation, the proportion of an observation that is due to subject-subject variability. One minus the intra-class correlation is the proportion that is due to all sources of error, including inter-reader variability.

The mean Sharp scores assigned by the 4 readers to 24 patients at baseline and at Month 6 and 12 were calculated. Because the primary endpoint was based on the change in Sharp score between baseline and 12 months, the mean change in Sharp core assigned by each reader was also calculated.

Table 1 Inter-reader Variability, Including DIP Joints

	(n = 24 patients)*						
		Total Sharp Score		Erosion Score		JSN Score	
	n*	Mean	SD	Mean	SD	Mean	SD
Raw Scores							
At baseline							
Reader 1	24	15.88	23.96	6.42	10.24	9.46	13.98
Reader 2	24	34.08	35.03	13.58	14.12	20.50	22.15
Reader 3	24	16.83	19.86	8.58	9.28	8.25	11.48
Reader 4	24	22.13	32.62	13.21	18.21	8.92	15.00
At Month 6							
Reader 1	21	16.76	25.07	6.67	10.74	10.10	14.65
Reader 2	21	35.71	34.81	14.52	14.42	21.19	22.10
Reader 3	21	17.48	19.70	8.43	8.76	9.05	12.13
Reader 4	21	25.71	34.25	15.48	19.27	10.24	15.74
At Month 12							
Reader 1	18	16.72	25.96	7.00	11.37	9.72	14.88
Reader 2	18	35.44	36.46	15.22	15.55	20.22	22.69
Reader 3	18	17.44	20.63	8.89	9.90	8.56	12.06
Reader 4	18	25.44	35.05	15.61	19.91	9.83	16.10
Change Scores†							
At Month 6							
Reader 1	21	0.29	0.85	0.05	0.59	0.24	0.54
Reader 2	21	0.29	2.59	0.24	2.17	0.05	0.67
Reader 3	21	0.29	1.95	-0.05	2.06	0.33	0.73
Reader 4	21	0.62	1.72	0.57	1.60	0.05	0.22
At Month 12							
Reader 1	18	0.67	2.17	0.61	1.91	0.06	0.42
Reader 2	18	0.67	3.80	1.00	3.03	-0.33	1.75
Reader 3	18	0.83	2.68	0.61	2.28	0.22	0.65
Reader 4	18	0.89	2.54	0.83	2.38	0.06	0.24
P-values for inter-reader difference							
Baseline		< 0.0001		0.0009		< 0.0001	
Month 6		< 0.0001		0.0002		< 0.0001	
Month 12		< 0.0001		0.0004		< 0.0001	
6-month change		0.8101		0.2957		0.2254	
12-month change		0.9724		0.7579		0.3444	

SD = standard deviation

* Three patients had only baseline films. Three additional patients had only baseline and 6-month films.

† Month 6 or Month 12 score minus baseline score.

From this analysis, it is evident that although the raw scores assigned differed between readers, the change scores assigned by the readers are similar. This indicates that though the readers may assign different raw scores, they are consistent in scoring change.

The intra-class correlation coefficients, based on the 24 patients whose films were read by all 4 readers, were determined for the baseline, Month 6, and Month 12 images as well as for the change scores.

Table 2 Intra-class Correlation (inter-reader),* Including DIP Joints

	(n = 24 patients)					
	Total Sharp Score		Erosion Score		JSN Score	
	ICC	Lower 95% CI†	ICC	Lower 95% CI†	ICC	Lower 95% CI†
ICC coefficient at:						
Baseline	0.8429	0.7549	0.7331	0.6042	0.8424	0.7541
Month 6	0.8686	0.7861	0.7361	0.5982	0.8790	0.8019
Month 12	0.8772	0.7915	0.7777	0.6430	0.8768	0.7909
Change at:						
Month 6	0.4879	0.3046	0.5804	0.4062	0.1300	-0.0220
Month 12	0.6237	0.4426	0.7244	0.5699	0.0476	-0.0939

CI = Confidence Interval

* Reader effect was considered as a fixed effect in the computation. ICC was calculated using formula ICC (3,1) of Shrout (1979).

† Lower bound of 95% 2-sided CI.

The intra-Class correlation is high, indicating that most of the variance is due to subject-subject variability rather than to other sources such as inter-reader variability. The change scores had lower intra-class correlation, however. The low intraclass values for the joint space narrowing change may be due to the small degree of change observed in this study.

Intra-reader Correlation:

The baseline, month 6 and month 12 radiographs were read twice and the precision of scores by individual readers was determines using the methods of Altman (1983) and Bland (1986). These results are summarized below.

Table 3 Consistency of Scores Between Two Reads for All Readers at 12 Months,* Including DIP Joints

Total Sharp Score, Erosion Score, and JSN Score									
		Baseline Mean		Mean Change Score Assigned at 12 Months		Discrepancy in Change Score (Read #2 - Read #1)			
	n	at Read #1	at Read #2	Read #1	Read #2	n†	mean	SD	95% CI for Mean
Total Sharp Score									
Reader 1	12	21.42	19.00	0.56	0.44	9	-0.11	0.60	-0.5730 – 0.3508
Reader 2	12	31.00	28.25	1.00	0.33	9	-0.67	1.41	-1.7537 – 0.4204
Reader 3	12	14.92	15.42	0.25	0.50	8	0.25	0.89	-0.4911 – 0.9911
Reader 4	12	32.25	29.25	1.10	1.00	10	-0.10	0.32	-0.3262 – 0.1262
Erosion Score									
Reader 1	12	9.08	8.25	0.22	0.33	9	0.11	0.33	-0.1451 – 0.3673
Reader 2	12	13.42	12.67	0.44	0.44	9	0.00	0.00	---‡
Reader 3	12	6.42	7.50	0.38	0.50	8	0.13	0.83	-0.5727 – 0.8227
Reader 4	12	16.92	17.00	0.90	0.90	10	0.00	0.47	-0.3372 – 0.3372
JSN Score									
Reader 1	12	12.33	10.75	0.33	0.11	9	-0.22	0.44	-0.5612 – 0.1167
Reader 2	12	17.58	15.58	0.56	-0.11	9	-0.67	1.41	-1.7537 – 0.4204
Reader 3	12	8.50	7.92	-0.13	0.00	8	0.13	0.35	-0.1706 – 0.4206
Reader 4	12	15.33	12.25	0.20	0.10	10	-0.10	0.32	-0.3262 – 0.1262

CI = Confidence Interval; JSN = joint space narrowing; SD = standard deviation

* Three patients had only baseline films; three additional patients had only baseline and Month 6 films.

† Number of patients with baseline and 12-month films that were read twice.

‡ Reader 2 read erosion change scores the same on Read #1 and Read #2 for all 9 patients.

The 95% confidence interval for mean discrepancy in change score for each reader included 0. Therefore, the readers were consistent in reading change with no evidence of systematic bias (due to time of reading).

An analysis using all 3 images for each patient that was read twice by a reader was also performed to assess intra-reader variability. The correlation between the first and second reads for each patient was calculated for each reader. The results are in the table that follows.

Table 4 Pearson Correlation Coefficients for Consistency in Scores Between Two Reads by the Same Reader

		(Including DIP Joints)		
	n*	Total Sharp Score	Erosion Score	JSN Score
Reader 1	31	0.9956	0.9948	0.9826
Reader 2	32	0.9921	0.9799	0.9668
Reader 3	31	0.8955	0.8061	0.9003
Reader 4	32	0.9779	0.9480	0.9922
All 4 readers	126	0.9797	0.9566	0.9681

* Three patients (of 24 patients re-read in the analysis of inter-reader correlation) had only baseline films.
Three additional patients had only baseline and Month 6 films.

This analysis shows a strong Pearson correlation between scores by the same reader.

In contrast to the intrareader correlations, the readings between reader pairs tended to be poorly correlated.

Table 5 Weighted Kappa Coefficients for Total Sharp Scores, Including DIPs - Using Ordinal Categories

Visit	Reader Pair 1/2	Reader Pair 1/3	Reader Pair 1/4	Reader Pair 2/3	Reader Pair 2/4	Reader Pair 3/4
Baseline	0.5229	0.8178	0.6910	0.6631	0.5610	0.6631
6 Months	0.5394	0.7593	0.7724	0.6647	0.6326	0.7025
12 Months	0.5017	0.7907	0.7293	0.6604	0.6087	0.6565

Table 6 Weighted Kappa Coefficients for Erosion Scores, Including DIPs - Using Ordinal Categories

Visit	Reader Pair 1/2	Reader Pair 1/3	Reader Pair 1/4	Reader Pair 2/3	Reader Pair 2/4	Reader Pair 3/4
Baseline	0.3952	0.6283	0.4815	0.6549	0.6066	0.5732
6 Months	0.3847	0.6003	0.5251	0.6239	0.6326	0.6326
12 Months	0.3407	0.6667	0.4983	0.5959	0.5970	0.5791

Table 7 Weighted Kappa Coefficients for Joint Space Narrowing Scores, Including DIPs - Using Ordinal Categories

Visit	Reader Pair 1/2	Reader Pair 1/3	Reader Pair 1/4	Reader Pair 2/3	Reader Pair 2/4	Reader Pair 3/4
Baseline	0.5573	0.7488	0.7321	0.5161	0.4870	0.6397
6 Months	0.5263	0.6837	0.7915	0.5013	0.5175	0.6628
12 Months	0.5700	0.6694	0.7899	0.5144	0.5200	0.6694

Reviewer's note: The inter-Reader correlations appear to be better when analyzed by ICC than by weighted kappa.

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June 23, 2003

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Dear Dr. Siegel:

Thank you for asking me to review the radiographic data and the radiographs themselves in the etanercept vs. placebo and psoriatic arthritis trial. George Mills, M.D. viewing arrangements were superb.

It is clear the study drug was effective for the most severely affective patients, but the addition of many mildly effected patient (22 had sharp scores of 0) made the overall average benefit one sharp score in the treatment group. Still only 4 study patient's vs 16 controls progressed 2 sharp scores during the course of the study. Only 20 study patients progressed at all vs. 42 controls. There is clearly some structural benefit to the use of Etanercept in some patients.

This despite several factors potentially limiting the ability of the study to find differences between study groups. The majority of the placebo patients received an excellent traditional treatment namely methotrexate which has been the gold standard. The duration of the trial (12 months) was relatively short. Dr. Gladman's doubling of patients with 5 severely affected joints (19 to 41% of patients) took five years. Some of the placebo patients were rolled over to the ETCP up to a month before the final x-rays were obtained.

To answer your specific questions I offer the following:

A. Face validity of sharp scores

X-rays of the hands offer only a glimpse of the extent and severity of the patient's arthritis which potentially can affect every joint including the entire spine. Face validity is modest, but still useful.

B. Prediction of progression

For the group taken as whole sharp scores were a poor predictor. But in the top 16 patients who progressed in both groups in comparison to the bottom 16 who did not sharp scores were higher (placebo 643 vs 440) (ETCP 700 vs 603).

C. Significant degree of change

The patient in my opinion would likely not notice one sharp score.

The question as to whether or not the company should be given "_____ the progression of structural damage" in the package insert is a difficult one. The benefits were real but modest in the ETCP group. The agency may wish to consider factors beyond the trial itself. These would include the general importance of radiographic trials in arthritis. To this clinician they are a gold standard. I doubt this addition to the package insert will any major effect on the prescribing pattern's of rheumatologists who are well aware of "one sharp score". Patients may be encouraged, but full informed consent before prescribing will be necessary. Costs and unknown risks still limit the use of the drug. The company is to be congratulated for studying a disease that is likely more common than generally thought and one that has received very little attention.

All things considered I favor granting the company the requested change, but this is a close and difficult decision.

Sincerely,

Frank B. Vasey, ~~M.D.~~
Professor and Director
Division of Rheumatology

FBV/kah

H. James Williams, MD
Consultation
June 25, 2003
Etanercept for the ——— of the progression of structural damage of active arthritis with psoriatic arthritis

I reviewed the Memorandum from Dr. Elektra Papadopoulos and Dr. Satish Misra and I reviewed selected radiographs with Dr. George Mills. My opinions are based on my understanding of psoriatic arthritis, etanercept and these reviews.

First, the Sharp score is a proven method for radiographic evaluation in rheumatoid arthritis. It should be applicable to any inflammatory erosive arthritis and I think it is a reasonable instrument to evaluate psoriatic arthritis. I think that changes in the Sharp score of 1 are within the error of the measurement. This is probably true for changes of 2. Changes of 3 are becoming meaningful but are still modest.

Psoriatic arthritis is not as predictable as rheumatoid arthritis. It has various presentations and it also varies widely in its manifestations. Some patients progress rapidly and some progress slowly or not at all. The rate of change is not predictable and not all patients will have change. This makes the disease more difficult to evaluate for ——— of structural damage than in rheumatoid arthritis where most patients will have some progressive xray changes.

If we use 3 as a cutoff for a meaningful Sharp score, there were no patients on etanercept that had progression or improvement over twelve months. For patients on placebo, twelve patients worsened and one improved. I personally could not have made a determination for improvement in the one patient (patient 76) based on the twelve month xray. I could not have performed a reliable Sharp score on the twelve month film which I thought was inadequate. If we use 2 as a cutoff, four etanercept patients worsened and five improved. For patients on placebo, sixteen patients progressed and the same patient showed improvement. These placebo patients drive the statistical differences seen.

I am also impressed that the single patient on etanercept with the arthritis mutilans subset had no progression while both arthritis mutilans patients on placebo had modest progression.

The differences in the Sharp scores after twelve months in most cases were modest but it was only a one year study. I would prefer to see a longer time period (perhaps two years) in the hope that greater differences in more patients would be seen. I am told that it is unlikely that more placebo data will become available.

The mean change in Total Sharp Score was statistically significant as reported in the Papadopouos/Misra review. I was impressed that twelve patients on placebo worsened (using 3 as a cutoff for meaningful significant difference in the Sharp score) and that none of the etanercept patients worsened even though the etanercept patients has more

severe radiographic disease at baseline and were therefore more likely to progress. The progression seen was generally modest but the time of observation was relatively short.

At the minimum, the sponsor deserves a statement in the label that etanercept has shown no radiographic progression at one year whereas a small number of placebo patients did have radiographic progression. However, if no further data is expected, I would think that the data would confirm a structural disease modifying indication. This is a little flavored by my knowledge of the data for disease modification in RA.

To: STN 103795/5102

From: George Q. Mills, M.D., Medical Officer DCTDA

Subject: Imaging Review Assessments

Re: Radiograph Review in support of

- Section 2.3.9 Image Scoring
- Section 2.4.2 Study Drug Exposure and Patients with Radiographic Data
- SGE Independent Assessments of Radiographic Scoring System & Subjects Scoring

Summary Comment

Supportive imaging review in support of the final review findings of Elektra Papadopoulos, M.D. has been performed (please see review of August 21, 2003).

In the course of the supportive imaging review assessments, no inconsistencies of interpretation by the independent reviewers were noted and the database and imaging presentation was found to be consistent and reproducible as compared to the electronic submission datasets.

The two SGE sessions were performed and independent reporting by both SGEs of these sessions are to be submitted.