ENBREL®
(etanercept)

FDA Arthritis Advisory Committee

April 11, 2000

THE ERA TRIAL

ENBREL® IN RHEUMATOID ARTHRITIS

Briefing Document

FDA Arthritis Advisory Committee

April 11, 2000

Immunex Corporation

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACR 20	ACR 20% response
ACR 50	ACR 50% response
ACR 70	ACR 70% response
ACR-N	ACR numeric response
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BUN	Blood urea nitrogen
CRF	Case report form
CRP	C-reactive protein
DMARD	Disease-modifying anti-rheumatic drug
ERA Trial	Enbrel rheumatoid arthritis trial
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HR-QOL	Health-related quality of life
JSN	Joint space-narrowing
kd	Kilodalton
LFT	Liver function test
MCS	Mental component summary of the SF-36
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PCS	Physical component summary of the SF-36
PO	Orally
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SC	Subcutaneous
SF-36	Short-Form Health Survey
TNF	Tumor necrosis factor, cachectin (previously known as TNFα)
TSS	Total Sharp score
VAS	Visual Analog Scale
WBC	White blood cell

EXECUTIVE SUMMARY

Study Drug ENBREL® (etanercept)

Company Immunex Corporation

Background

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases, with a prevalence of approximately 1% in Caucasian populations. In spite of treatment, this disease generally progresses to produce disability and substantial functional loss in more than 50% of patients, resulting in occupational disability or unemployment.

The structural damage that characterizes RA begins early in the course of active disease. Based on this, aggressive intervention during the initial stages of the disease is now viewed as critical to disease management (ACR Guidelines1996).

The Sharp scoring system, a sensitive, reproducible and validated measure of joint damage, was used as the scoring system in the Enbrel RA trial (ERA trial). The total Sharp score (TSS) is composed of the sum of the joint erosion and joint space narrowing (JSN) scores. The rate of change in the total score is a measure of the severity of disease occurring between x-rays.

Weekly methotrexate (MTX) (up to 20 mg orally) is an established treatment approved by the United States Food and Drug Administration (FDA) in 1988 for improvement of signs and symptoms of RA. Over the past decade, MTX has become the leading therapeutic choice of rheumatologists in the United States for the treatment of patients with RA. Although MTX is approved for reduction of signs and symptoms of RA, it has been shown in multiple studies to prevent structural damage (Weinblatt 1993; Schiff 1999; Strand 1999).

Rationale

Tumor necrosis factor (TNF) is an inflammatory cytokine that is overproduced in the joints of patients with RA (Saxne 1988). Excess TNF triggers cells through surface TNF receptors to produce a cascade of inflammatory and damaging effects. As an inflammatory mediator, TNF contributes to the pathogenesis of synovitis and joint destruction in RA. TNF induces inflammation by upregulating the production of inflammatory cytokines (IL-1 and IL-6). TNF also increases cell migration by increasing the production of cellular adhesion molecules (E-selectin, ICAM-1) and increases tissue remodeling by matrix-degrading proteases (Lorenz 1996; Paleolog 1996; Braunstein 1994; Tak 1996). At least 2 effects mediated by excess TNF, the activation of osteoclasts the induction of metalloproteinases, are thought to have a role in eroding bone and destroying cartilage.

Etanercept (Enbrel®) is an entirely human protein, comprised of 2 identical molecules of the tumor necrosis factor (TNF)-binding portion of p75 TNF receptor fused to the Fc portion of a human IgG1. Enbrel has been shown to bind TNF with high affinity and inhibit TNF-mediated processes.

Current Indications and Dosage

Enbrel has been studied in RA clinical trials since 1992. Current indications approved by FDA are:

- Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying drugs (DMARDs). Enbrel can be used in combination with MTX in patients who do not respond adequately to MTX alone [November 1998].

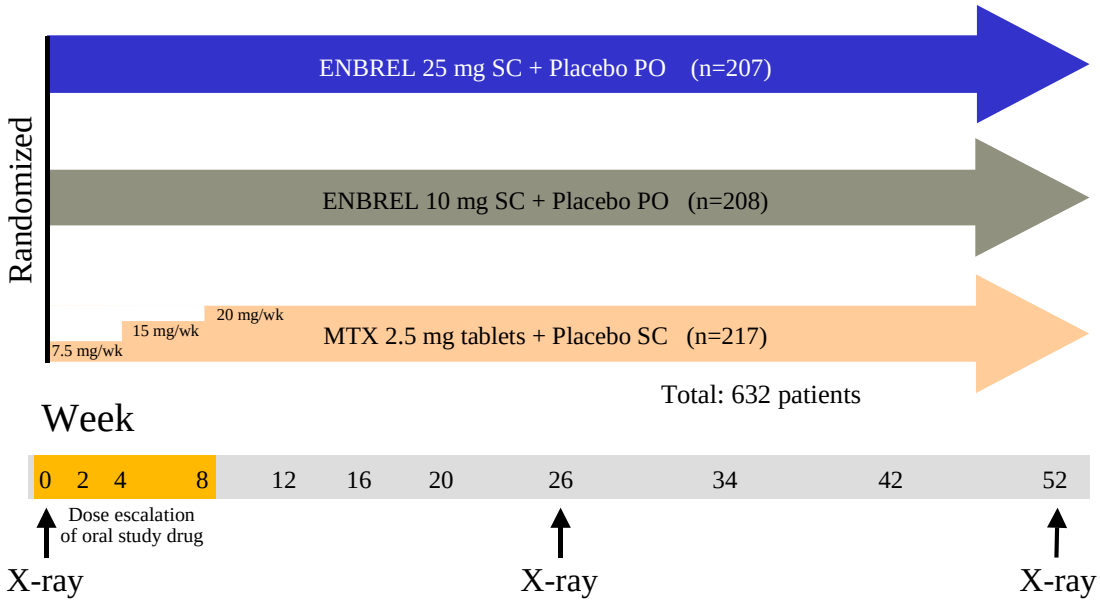
- Reduction in signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs [May 1999].

The recommended Enbrel dose for adult patients is 25 mg given twice weekly as a subcutaneous (SC) injection. The pediatric dose of 0.4 mg/kg given SC twice weekly is approximately equivalent to the adult dose on a per kilogram basis.

The efficacy and safety of Enbrel treatment was directly compared to MTX treatment in the ERA trial. The two primary objectives were to evaluate the efficacy of Enbrel for the prevention of structural damage and for the improvement of signs and symptoms of RA in MTX-naive patients with RA.

Study Design

This was a randomized, multicenter, double-dummy, active-control, Phase III study comparing Enbrel 10 mg, Enbrel 25 mg, and optimized oral MTX (20 mg/week) in adult patients with active RA who were early in their disease course (≤ 3 years) and had not previously received MTX. The patient population was selected to have highly active disease and be at risk for rapid radiographic progression. The study design is summarized in the following figure.



Study Design

MTX and placebo tablets were rapidly dose-escalated over 8 weeks in order to provide MTX with the best chance to perform optimally. Patients who discontinued study medication were provided with standard therapy by their physicians and remained in the study for evaluation.

RA studies designed to show benefit in prevention of structural damage have often utilized a placebo group as the comparison arm. In this trial, all patients received an active treatment. Per specific inclusion/exclusion criteria, patients selected for trial participation were at risk of rapid joint erosion; 88% were rheumatoid factor (RF) positive; 87% had erosions at baseline; the mean swollen joint count was 24; and approximately 60-70% of patients had elevated acute phase reactants (mean ESR = 40 mm/hr, mean CRP = 3.7 mg/dL). Because the patient population was enriched for active, rapidly progressive disease and given the evidence in the literature that early, aggressive intervention is necessary in RA patients, a placebo-only treatment arm was not considered feasible. The study was performed with an active (MTX) control arm.

The ERA trial was originally designed, sized, and conducted as a superiority trial. Statistical considerations of size and power for the study were based on demonstrating superiority in preventing erosions by change in Sharp erosion score over 12 months. After all patients had been accrued and randomized, but prior to study completion and unblinding, the protocol was amended to change the primary structural damage endpoint to non-inferiority of Enbrel 25 mg to MTX with respect to TSS at 12 months. The primary endpoint was changed because data became available from 2 large active-controlled trials studying leflunomide (Strand 1999; Schiff 1999). These trials clearly demonstrated that MTX prevented structural damage as measured by TSS. Since MTX is considered by most rheumatologists to be the “gold standard” DMARD and with solid evidence demonstrating that MTX prevents radiographic damage, it became important to establish equivalence to MTX. The term “equivalence”, rather than non-inferiority, is used throughout this document. The equivalence endpoint was defined as maintenance by Enbrel 25 mg of 70% of the expected benefit of MTX (4 total Sharp units).

The primary efficacy endpoints were:

- Prevention of structural damage
  - Original - superiority in erosion score at 12 months
  - Final - equivalence in TSS at 12 months

- Improvement in signs and symptoms of RA

  – Superiority as measured by the area under the curve of an index (ACR-N AUC) derived from the American College of Rheumatology (ACR) definition of improvement over 6 months.

Demographics

A total of 632 patients received at least one dose of active study drug, including 217 patients in the MTX group, 208 patients in the Enbrel 10 mg group, and 207 patients in the Enbrel 25 mg group. At baseline, the 3 treatment groups were well balanced with regard to all demographic variables. The overall mean age was 50 years, with a range of 19 to 84 years. Eighty-eight percent of the patients in this trial were RF positive. The mean joint count at baseline was 24 swollen and 31 tender joints. At baseline, 88% of patients had erosions, consistent with an increased risk for rapid progression of joint damage.

Study Completion

This was an intent-to-treat trial. Patients were analyzed according to the group to which they were randomized regardless of whether they discontinued study drug prior to the completion of the study. Most of the patients who discontinued study drug remained in the study for their scheduled study evaluations. The percent of patients in each group who completed 1 year of study evaluations was 93%, 90%, and 93% in the MTX, Enbrel 10 mg, and Enbrel 25 mg groups, respectively. Seventy-nine percent of MTX patients remained on study drug at the 12-month evaluation compared to 80% and 85% of Enbrel 10 and 25 mg patients, respectively. Significantly more MTX-treated patients than

Enbrel patients discontinued study drug due to adverse events: 10% in the MTX group, compared to 4% in the Enbrel 10 mg group and 5% in the Enbrel 25 mg group (p = 0.016, MTX vs all Enbrel).

Summary of Efficacy

Enbrel Prevents Structural Damage in RA

The primary equivalence analysis shows Enbrel 25 mg to be at least equivalent to MTX in preventing progression of disease measured radiographically. In order to demonstrate an effect on prevention of structural damage, Enbrel 25 mg was required to preserve at least 70% of the expected benefit of MTX.

The mean changes in TSS over 12 months were 1.3, 1.4, and 0.8 units for the MTX, Enbrel 10 mg, and Enbrel 25 mg groups, respectively. The upper bound of the 1-sided 95% confidence interval for the difference between Enbrel 25 mg and MTX was 0.16 total Sharp units/year, well within the prospectively defined threshold of 1.2 total Sharp units/year. Enbrel 25 mg is estimated to have 113% of the predicted MTX treatment effect and with one-sided 95% confidence it preserves at least 96% of the predicted MTX treatment effect. Another perspective indicating the robustness of the results is that the equivalence criterion would have been met even if the MTX to placebo effect used was only 0.23 Sharp units. Thus, the primary equivalence endpoint was not only achieved, but was exceeded by a comfortable margin.

Analysis of the superiority endpoint demonstrated that Enbrel 25 mg was significantly more effective than MTX in preventing erosions. The mean change from baseline in erosion score at month 12 for MTX patients was 1.03 units, compared to 0.90 units in Enbrel 10 mg patients, and 0.47 units in Enbrel 25 mg patients (overall p = 0.005, pairwise Enbrel 25 mg vs MTX p = 0.002). In the Enbrel 25 mg group, 72% had no progression in erosion score at 12 months, compared to 60% in the MTX group (p = 0.007). The three treatment groups showed similar low rates of progression of JSN.

MTX, rapidly escalated and given at 20 mg/week, also performed well in this study, particularly when compared with the literature. This is even more noteworthy if one takes into account the highly active characteristics of the RA in this patient population.

Enbrel Reduces Signs and Symptoms of RA

Enbrel 25 mg was effective in reducing signs and symptoms of RA in these patients. The mean ACR-N AUC over 6 months was 11.5, 13, and 15.3 units (ACR-N•year) for the MTX, Enbrel 10 mg, and Enbrel 25 mg groups, respectively (overall $p = 0.006$, pairwise Enbrel 25 mg vs MTX $p = 0.002$).

The dose of MTX was escalated in this study from 7.5 mg to 20 mg per week by week 8. This dose escalation is more rapid than has been utilized in most previous clinical trials. MTX was administered in this way to ensure that the highest efficacy of MTX therapy would be observed. Despite the rapid dose escalation of MTX, both Enbrel groups had a more rapid clinical response.

The other clinical endpoints in this study corroborate the primary clinical endpoint and confirm the efficacy of Enbrel in the treatment of signs and symptoms of RA. For all of the individual disease activity parameters, improvement was rapid and sustained.

Clinical improvement correlated with lack of radiographic progression.

Summary of Safety

The safety of Enbrel was also compared to that of MTX, commonly considered the most effective DMARD for treating patients with RA. As in previous controlled trials of patients with longstanding RA and in a long-term open-label safety study (Appendix A), this 1-year study in patients with early active rheumatoid arthritis demonstrates that Enbrel is generally safe and well tolerated and provides a good benefit-to-risk profile. In this study of patients with active RA treated within 3 years of diagnosis who had not previously been treated with MTX, the safety profile was similar to that described in

previous studies of Enbrel in patients with long-standing, active RA who had not adequately responded to or had failed DMARDs.

Adverse Events

The rate and frequency of adverse events seen in this trial were lower in both groups of patients receiving Enbrel than in patients receiving MTX. These adverse events included both common and serious toxicities attributable to MTX, including nausea, rash, mouth ulcers, epistaxis, and potentially fatal pneumonitis. The latter was observed in 3 patients (1.4%) receiving MTX (who were hospitalized for 8-9 days each) but in none of the patients receiving Enbrel.

As in previous trials, injection site reaction (ISR) was the most common adverse event reported in patients receiving Enbrel (34%). The ISRs that were observed were all Grade 1 or Grade 2 in intensity, typically lasted 3 days, and resolved without therapy. Only 1 patient withdrew from the study because of an ISR.

Deaths

There were 2 deaths in this study, 1 of metastatic lung cancer in the Enbrel 10 mg group and 1 of perioperative complications following emergency repair of a pre-existing aortic aneurysm in the Enbrel 25 mg group. Both deaths were considered by the Investigators to be unrelated to Enbrel.

Infection

The overall rate of all types of infection was higher in patients receiving MTX than in those receiving Enbrel (1.91 events per patient-year in the MTX group versus 1.54 in each Enbrel group, $p = 0.006$). Infections that required hospitalization or intravenous antibiotics were infrequent and occurred in 6 patients in the MTX group, 2 in the Enbrel 10 mg group, and 4 in the Enbrel 25 mg group. Two patients in the MTX group discontinued study drug due to serious infections, compared to 2 patients in the Enbrel 10 mg group and 1 patient in the Enbrel 25 mg group. There were no opportunistic infections and no deaths associated with infections.

Malignancy

There was no evidence of an increased rate of malignancy in any treatment group when compared to national rates in the general population (National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER]). There were 2 cases in the MTX group (colon and bladder), 2 cases in the Enbrel 10 mg group (breast and lung), and 3 cases in the Enbrel 25 mg group (carcinoid lung, Hodgkin's disease, and prostate).

Laboratory Results

There were no unexpected abnormalities in laboratory results in any of the treatment groups. When abnormal laboratory tests that occurred at any time in the study were summarized, elevated liver enzymes (ALT and AST) and low lymphocyte counts occurred at higher frequencies in the MTX group, as would be expected. Transient neutropenia (primarily absolute neutrophil counts $\geq$2000 but less than 1500 cells/cmm), without clinical sequelae, was seen in 16% of patients in the Enbrel 25 mg group, compared to 8% in the MTX group and 10% in the 10 mg group. The low frequency of abnormal laboratory results in the Enbrel groups is consistent with earlier trials.

Antibody to Enbrel

Three percent of patients in the Enbrel treatment groups developed antibodies to Enbrel. None of the antibodies had neutralizing activity, and there was no relationship between safety or efficacy and the presence or absence of these antibodies.

Conclusions

The results of this active controlled trial, which directly compared Enbrel to optimal oral MTX therapy, demonstrate that Enbrel prevents structural damage and improves signs and symptoms of RA. The primary efficacy endpoints are summarized in the following table.

Summary of Primary Efficacy Endpoints

	MTX	Enbrel		Enbrel 25 mg vs MTX	
		10 mg	25 mg	p value	Goal
STRUCTURAL DAMAGE					
Equivalence Endpoint (progression rate in TSS over 12 months)	1.3	1.4	0.8	NA*	Achieved
Superiority Endpoint (progression rate in erosion score over 12 months)	1.03	0.90	0.47	0.002	Achieved
SIGNS AND SYMPTOMS					
ACR-N AUC over 6 months	11.5	13.0	15.3	0.002	Achieved

***upper limit of one-sided 95% CI = 0.16 which is less than prespecified equivalence limit of 1.2**

Enbrel 25 mg met prospectively defined criteria to demonstrate both equivalence to MTX for preventing structural damage using the TSS and superiority to MTX in preventing erosions using the erosion score alone. These findings support the conclusion that Enbrel is an important treatment option that will prevent structural damage in RA, and justifies the classification of Enbrel as a "DMARD".

Furthermore, as shown in previous studies of RA patients with long-standing disease, Enbrel also provides significant benefit in reducing the signs and symptoms of patients with early active RA. Compared to patients treated with MTX, patients treated with Enbrel 25 mg had a faster onset of clinical response and that response was sustained over 12 months.

Enbrel is well-tolerated and has a good benefit-to-risk profile.

Enbrel at 25 mg provides rapid, substantial, durable, and comprehensive improvement for patients with active RA and is a valuable addition to treatment options for patients and physicians to use in early as well as long standing active RA.

Proposed Indications

- Enbrel is indicated for prevention of structural damage in patients with rheumatoid arthritis.

- Enbrel is indicated for reduction in signs and symptoms of rheumatoid arthritis.

1.0 Introduction

1.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) occurs with a prevalence of approximately 1% in developed countries (Hoffman 1992; Gabriel 1999). RA occurs most commonly in women between ages 35 and 50, with an estimated annual incidence per 100,000 people of 22 in men and 60 in women (Chan 1993). RA typically presents with pain, stiffness, and swelling in the small joints of the hands and feet. Large joints are also affected in most cases, and often the disease has extra-articular involvement, including cutaneous, pulmonary, ocular, and vascular manifestations. Additional clinical manifestations of the disorder include chronic pain and fatigue. There is progressive loss of function in affected joints due to deformities and damage to supporting joint structures (Harris 1990; Vaughan 1993; Odeh 1997; Jaffe 1992).

RA has a detrimental impact on many aspects of the lives of affected patients. Over 50% of RA patients experience substantial functional loss within 5 years of onset or diagnosis, resulting in occupational and vocational disability with resultant unemployment and decrease in quality of life. The life expectancy of RA patients is decreased an average of 4 to 10 years compared to the general population due to disease-related infections and renal, respiratory, and gastrointestinal disorders (Hoffman 1992; Schumacher 1988). Depression is common.

The importance of early treatment of RA has long been well recognized, and in the past 10 years has been emphasized by better treatment results with the more widespread use of more effective therapy. It is well documented that structural damage begins within the first year in most patients (van der Heijde 1995) and progresses steadily over many years (Wolfe, Sharp 1998). Certain patients with RA are known to progress rapidly; particularly those who are RF positive, have many active joints, have increased levels of acute phase reactants, and show early erosive changes on x-ray (van der Heijde 1995; Matsuda 1998; Plant 1998; Stenger 1998; Wolfe 1998). Radiographic progression has

been reported by some investigators to be linear (Plant 1998, Wolfe 1998) although this is disputed by others.

The current American College of Rheumatology (ACR) guidelines for the management of RA (ACR 1996) states that DMARD therapy should not be delayed for more than 3 months in patients who, despite treatment with NSAIDs, continue to have joint pain, significant morning stiffness, active synovitis, or persistent elevations of acute phase reactants. Though it is not known which is the best initial DMARD for RA, hydroxychloroquine or sulfasalazine are often the initial selection for patients with milder disease. For patients with moderate to severe disease as evidenced by the presence of rheumatoid factor (RF) or erosions, many rheumatologists prescribe MTX as the first DMARD or a combination of MTX with another DMARD.

1.2 Measurement of Radiographic Damage in RA

Joint erosions and progressive joint space narrowing (JSN), due to destruction of articular cartilage by pannus, are both important in documenting the progression of RA. Slowing radiographic progression of RA has become an established surrogate marker for overall patient benefit (FDA 1999). Several validated methods for assessing the extent of radiographic damage in RA have been described (Larsen, 1977; Genant, 1983; Rau, 1998; Sharp, 1971; Sharp, 1985; van der Heijde 1992). Radiographic scores on serial x-ray films, when related to the time interval between films, express the rate of progression of structural damage and are a powerful tool for determining the efficacy of therapeutic agents.

The two most commonly used radiographic indices are those of Larsen and Sharp (Larsen 1977; Sharp 1971; Sharp 1985). In the Larsen method, joints are graded from 0 (no damage) to 5 (mutilating changes). The assignment of grade considers initially only the severity of erosions. In a recent modification Larsen has reported that JSN is also considered. The Sharp method assigns separate scores for erosions and JSN. Erosions are scored on a scale from 0 to 5 and JSN is scored on a scale from 0 to 4. The TSS is the

sum of erosion and JSN scores. Although both methods are validated, the Sharp method has been reported by some to be more sensitive to change over time (Cuchacovich 1992) and more sensitive and reproducible in patients with early RA (Plant 1994). The ERA trial used a modification of the original Sharp method that scores the feet as well as the hands and wrists (van der Heijde 1992). Differences in scoring methods have made it difficult to compare scores between various studies.

1.3 Proposed Indications

Protocol 16.0012 was designed to add the new indication of "prevention of structural damage" and support a modification in the "signs and symptoms" indication.

1.3.1 Prevention of Structural Damage Indication

According to FDA Guidance Document (1999), the outcome measures that may be used to grant the "prevention of structural damage" indication includes:

1. Slowing of x-ray progression, using either the Larsen, the modified Sharp, or another validated radiographic index.

2. Prevention of new x-ray erosions - maintaining an erosion-free state or preventing new erosions.

The guidance indicates that the claim should be based on x-rays after 12 months of treatment and that all randomized patients should have films taken at baseline and 12 months regardless of whether they are continuing treatment.

Previous Enbrel trials did not include radiographic evaluations and therefore this indication is not presently included in the present package insert. The proposed language for the prevention of structural damage indication as outlined in FDA Guidance for Industry (1999) is: "XXXX is indicated for prevention of structural damage in patients with rheumatoid arthritis."

The best approach to designing an RA trial that selects patients with active rapidly progressing disease is controversial. Options include inclusion of a placebo arm for the entire trial length, inclusion of a placebo arm for a shorter period (i.e. 4 months) with an early escape of non-responders to active treatment, or use of an active control arm. Each option entails a unique set of issues. For placebo-controlled trials, these issues include high withdrawal rates and missing data and the questionable utility of radiographic data from patients with a relatively short treatment period on placebo. For actively controlled trials, the assessment of the efficacy of the agent chosen as the active control must be obtained from the literature. Taking into consideration the selection of a patient population with highly active disease and a high probability of radiographic progression, and the concerns regarding withholding appropriate treatment, a placebo arm was not included. The ERA trial was designed as an active-controlled trial, comparing Enbrel to MTX.

The ERA trial was originally designed, sized, and conducted as a superiority trial. Statistical considerations of size and power for the study were based on demonstrating superiority in preventing joint erosions. The primary endpoint was changed because data became available from 2 large active-controlled trials studying leflunomide (Strand 1999; Schiff 1999). These trials clearly demonstrated that MTX prevented structural damage as measured by TSS. Since MTX is considered by most rheumatologists to be the “gold standard” DMARD and with solid evidence demonstrating that MTX prevents radiographic damage, it became important to establish equivalence to MTX. The amendment did not change the conduct of the study; only the analysis plan was modified. The results of both of these analyses are presented in this summary.

1.3.2 Signs and Symptoms Indication

The current wording of the signs and symptoms indication in the Enbrel Package Insert is: "Enbrel is indicated for the treatment of signs and symptoms of moderately to severely active RA in patients who have an inadequate response to one or more DMARDs."

The proposed modification of the signs and symptoms claim is: "Enbrel is indicated for the treatment of signs and symptoms of RA." This modification will provide physicians with another treatment when prescribing a first "DMARD" for patients with RA.

Cumulative clinical response, as measured by the ACR-N AUC, was the primary clinical endpoint. This endpoint measures cumulative symptom relief and takes into account the more rapid responses seen with Enbrel therapy.

1.4 Expected Rates of Radiographic Progression

1.4.1 Expected Progression Rates in Non-DMARD-Treated Patients

The prevention of structural damage endpoint is based on the assumption that newly diagnosed RA patients with erosive, actively progressive disease will progress by 6 total Sharp units/year if they are untreated, and by 2 units/year if treated with MTX.

Data summarized in the following table are primarily derived from control arms of randomized trials where the controls used were placebo or agents less effective than MTX. Demographic data describing the patient population has been included where possible so the reader may compare the risk factors for aggressive disease between patient groups.

Table 1.4.1A Radiographic Progression by Sharp Method in Patients Receiving Placebo or Less Effective DMARDs*

Study	Treatment Group	N	Study Length	Mean Duration of RA	Mean CRP mg/dL	% Pts. RF +	Baseline Swollen Joint Count	Projected Yearly Progression†	Total Sharp Score	
									Baseline	Change over 12 Months
Jeurissen	**Azathioprine (100 mg/day)**	**33**	48 wks	**9.4 yr**	**5.0**	**100%**	**19**	**6.4**	**60.5**	**7.6**
1991	MTX (15 mg/wk)	30		13 yr	3.9	94%	19	4.9	62.7	4.0
Hannonen	**Placebo**	**40**	48 wks	**6 mo**	**2.4**	**68%**	**5**	**4.6**	**2.1**	**7.1**
1993	SSZ (2 g/d)	37		5 mo	2.7	66%	7	4.9	1.9	3.5
Weinblatt ‡	**Auranofin (6-9 mg/day)**	**72**	0.7 yr	**5.6 yr**	--	**78%**	**18**	**2.6**	**14.4**	**4.4**
1993	MTX (15 mg/wk)	95		6 yr	--	78%	21	2.9	16.7	1.4
Paulus (in press)	**NSAIDs**	**824**	**1.9 yr**	**3.6 yr**	**2.2**	**67%**	**22**	**5.9**	**20.7**	**5.1**

MTX = methotrexate, SSZ = sulfasalazine

*comparator groups for each study also provided, placebo or less effective DMARD shown in red

† calculated by dividing baseline score by disease duration

‡ 36 week change scores adjusted for 1 year estimate

1.4.2 Expected Progression Rates in MTX Treated Patients

Compared to placebo or less effective "DMARDs", MTX has been noted to have a relative benefit of between 47% to 68%; MTX reduces radiographic progression by one-third to one-half of that observed in untreated patients. These data are summarized in the following table.

Table 1.4.2A Radiographic Progression by Sharp Method in MTX-Treated Patients

Study	Treatment Group	N	Study Length	Duration of RA	12 Month Change in TSS	MTX Difference†	Relative Benefit‡
Jeurissen 1991	**MTX (15 mg/wk)**	**30**	48 wks	13 yr	**4.0**	**3.6 units**	**47%**
	Azathioprine	33		9.4 yr	7.6		
Weinblatt 1993§	**MTX (15 mg)**	**95**	**0.7 yr**	**6 yr**	**1.4**	**3.0 units**	**68%**
	Auranofin (6-9 mg/day)	72		5.6 yr	4.4		
Strand 1999	**MTX (12.5 mg/wk)**	138	1 yr	**6.5 yr**	**0.9**	**1.3 units***	**60%**
	LEF (20 mg/day)	131		7 yr	0.5		
	Placebo/LEF**	83		6.9 yr	2.2		

MTX = methotrexate, LEF = leflunomide
† MTX minus comparator
‡ Calculated as MTX difference / comparator change in TSS
* MTX - placebo
** 44% of the placebo patients crossed over to leflunomide for up to 8 months
§ 36 week change scores adjusted for 1 year estimate

Although the package insert for MTX does not include the indication for prevention of radiographic progression, it has been the therapeutic "gold standard" DMARD used by rheumatologists for the past decade. The ACR "Guidelines for Management of RA" state that MTX is the DMARD with the most predictable benefit (ACR 1996).

A review of 27 clinical trials conducted in the last decade indicates that the dose of MTX administered to patients with RA has tended to increase over time. This is illustrated in the following figure.

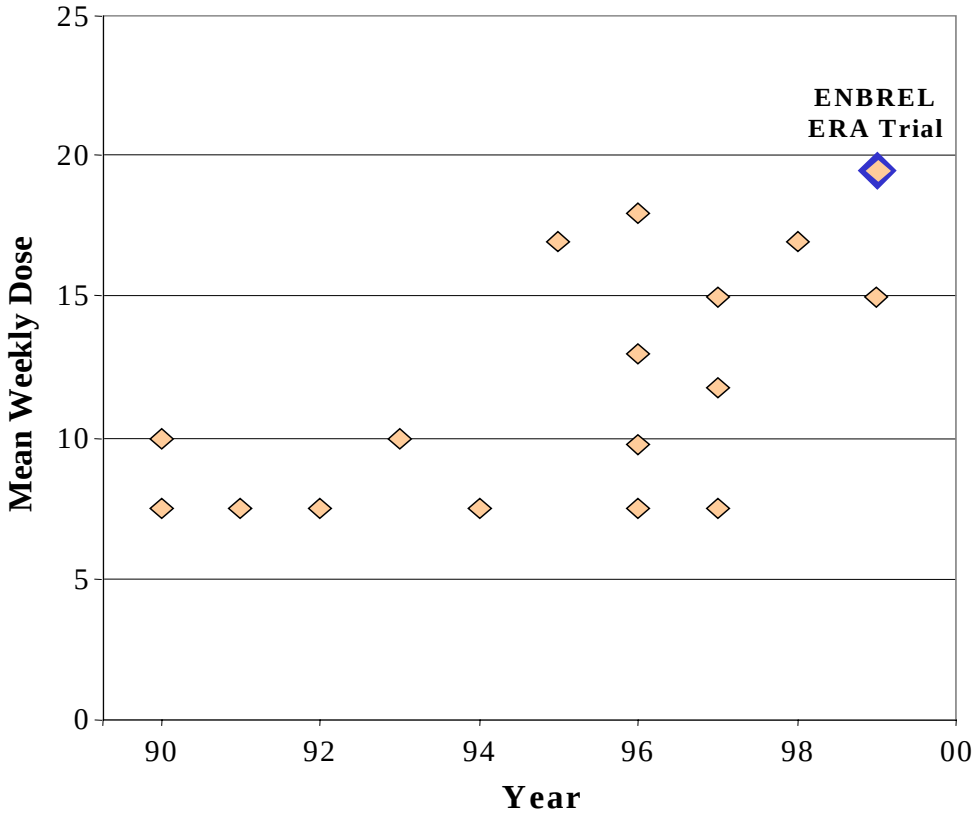


Figure 1.4.2A Mean MTX Doses over the Last 10 Years

The higher oral doses of MTX used today are generally believed to be more effective than lower oral doses in inhibiting radiographic progression (Sanders 2000), and therefore the 20 mg/week dose of MTX was chosen for the ERA trial.

1.5 Rationale for the Current Study

Tumor necrosis factor (TNF) is an inflammatory cytokine that is overproduced in the joints of patients with RA (Saxne 1988). Excess TNF combines with cell surface TNF receptors to produce a cascade of damaging and inflammatory effects. As an inflammatory mediator, TNF appears to contribute to the pathogenesis of synovitis and joint destruction in RA. TNF induces inflammation by upregulating the production of inflammatory cytokines (IL-1 and IL-6). TNF also increases cell migration by increasing the production of cellular adhesion molecules (E-selectin, ICAM-1) and increases tissue

remodeling by matrix-degrading proteases (Lorenz 1996; Paleolog 1996; Braunstein 1994; Tak 1996). TNF stimulates osteoclast formation and that, together with the increase in production of metalloproteinases, is partially responsible for the structural damage of the inflamed RA joint.

Since TNF and IL-1 both induce the matrix metalloproteinases, MMP-1 and MMP-3, neutralization of TNF might be expected to decrease induction of these potent proteases. MMP-1 and MMP-3 levels are elevated in patients with RA. Treatment with an anti-TNF monoclonal antibody resulted in a significant decrease in serum MMP-3 levels (Brennan 1997), suggesting that TNF inhibition in early disease may prevent the proteolytic joint and cartilage destruction that is characteristic of RA.

There are 2 distinct cell surface receptors for TNF: the 55 kilodalton (kd) (p55) and the 75 kd (p75) TNF receptors (TNFR). It was hypothesized that a recombinant TNF receptor that was able to bind TNF with high affinity could act as a competitive inhibitor of TNF-mediated inflammatory reactions. Recombinant human TNFR:Fc (Enbrel) is an all human protein comprised of 2 identical molecules composed of the TNF-binding portion of p75 TNFR fused to the Fc portion of a type 1 human immunoglobulin (IgG1). Enbrel has been shown to bind TNF with high affinity and inhibit TNF-mediated processes.

The first randomized, blinded trial in the development program for Enbrel in RA began in 1993. Initial studies concentrated on the safety and efficacy of Enbrel in patients with long-standing RA who had an inadequate response to available therapy. For licensing studies, the efficacy of Enbrel was evaluated in 3 controlled trials using the ACR 20 response criteria. The patients in these studies had a mean duration of RA of approximately 12 years and had received approximately 3 DMARDs prior to the study. Results of the 3 studies are shown in the following figure.

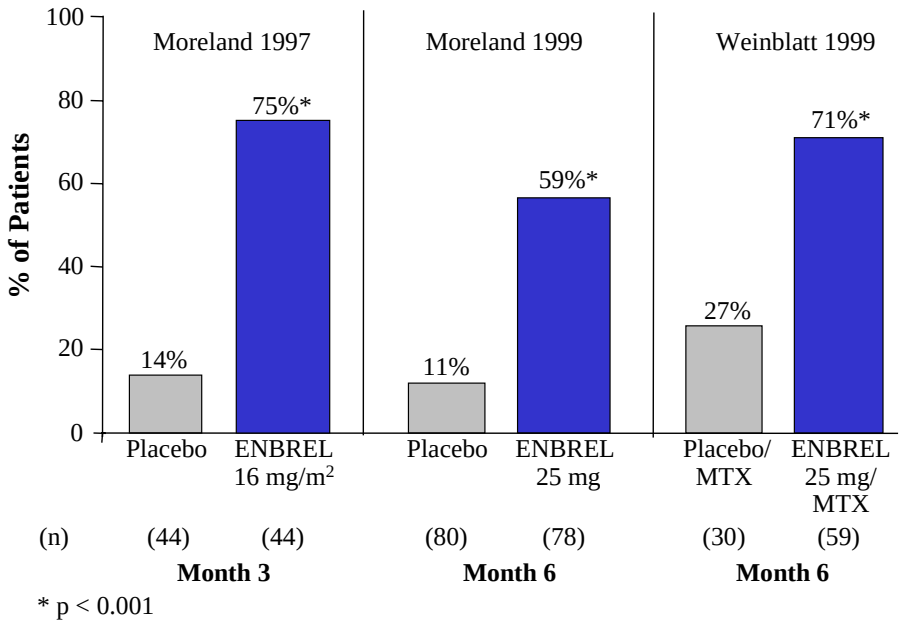


Figure 1.5A ACR 20 Responses in Patients with Controlled Trials of Patients with Long-Standing RA

Based on these studies, Enbrel was approved in November 1998 for use in the reduction of signs and symptoms of moderately to severely active RA in adult patients who had an inadequate response to one or more DMARDs for use with or without MTX. Subsequently, a multicenter, randomized, double-blind, placebo-controlled study in 69 pediatric patients between the ages of 4 and 17 years demonstrated that Enbrel can significantly decrease disease activity in patients with polyarticular-course juvenile RA (JRA). In May 1999, Enbrel was approved for use in pediatric patients who had an inadequate response to one or more DMARDs. The recommended dose of Enbrel for adult patients is 25 mg given twice weekly as a subcutaneous (SC) injection and the pediatric dose is 0.4 mg/kg SC twice weekly.

Enbrel has been administered to a large number of patients, both in clinical trials and by prescription. It is estimated that Enbrel has been prescribed to over 65,000 patients since the market introduction in 1998. The following table summarizes exposure and duration of Enbrel therapy in global RA clinical trials.

Table 1.5A Enbrel Exposure in Global Clinical RA Trials*

Length of Treatment	Total Number of Patients	ICH Guidelines
Any	1841*	1500
≥ 6 months	1531	300-600
≥ 12 months	1425	100
≥ 24 months	436	
≥ 36 months	53	

* an additional 700 patients with other diseases have received Enbrel in trials

Most current RA therapies were not specifically developed to treat RA and they have broad effects. Current RA therapies used to treat active RA include immunosuppressive agents (azathioprine, cyclosporine A), antimetabolites (MTX, leflunomide), and other drugs that control disease symptoms through mechanisms that are unknown (gold salts, anti-malarials, corticosteroids). All of these treatments are effective but may be limited by lack or loss of efficacy over time and/or dose limiting toxicities.

MTX is the DMARD with the highest likelihood of continued use over time (Madhok 1999). Although many of the toxicities of MTX may be considered mild to moderate, some, such as pneumonitis, pancytopenia and hepatic cirrhosis, are life threatening and unpredictable. Some adverse events require reductions in the dose of MTX so that it is no longer efficacious. Hepatic toxicity increases with cumulative exposure to MTX, and patients must comply with frequent laboratory monitoring. MTX is contraindicated in women of childbearing potential due to risk of early abortion and teratogenicity. The most recently approved DMARD, leflunomide, has been shown to be more effective than placebo in preventing radiographic progression. Its effectiveness is similar to MTX, as is its adverse event profile. Although these DMARDs are generally well tolerated, dose limiting toxicity or lack of response can limit their utility. There is need in the therapeutic armamentarium for new agents such as Enbrel, which will provide additional options for rheumatologists and patients.

The efficacy and safety of Enbrel had not been previously studied in a group of adult patients with early active RA who had never received MTX. In addition, the ability of Enbrel to prevent structural damage as measured by radiographic progression of disease had not been previously tested.

2.0 Study Design

2.1 Objectives

The ERA trial was a 12-month, 3-treatment arm, double blind trial in 632 MTX-naive patients with RA. Patients received both injections and tablets and were randomized to receive either twice-weekly subcutaneous Enbrel (10 or 25 mg) or weekly oral MTX (dose escalated to 20 mg over 8 weeks) plus the respective placebo therapies. Patients were stratified by duration of disease (<18 months or 18 – 36 months since diagnosis) prior to randomization. The study design is illustrated in the following figure.

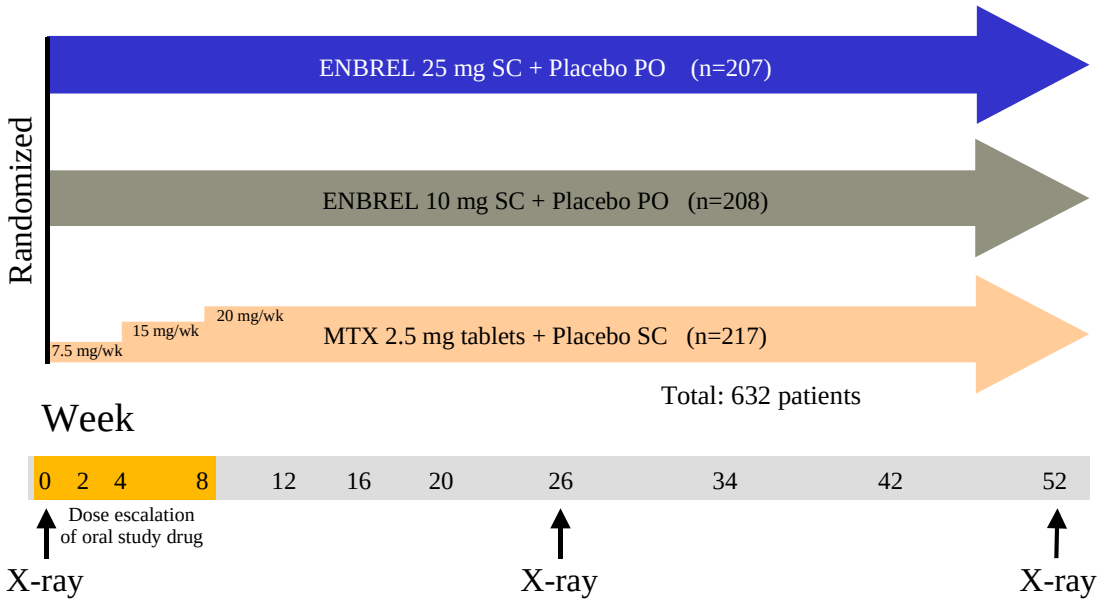


Figure 2.1A Study Design

The safety and efficacy of Enbrel were directly compared to optimally dosed MTX. The two primary objectives were to evaluate the efficacy of Enbrel on prevention of structural damage and on the signs and symptoms of RA.

2.2 Eligibility Criteria

Patients were eligible for entry into the study based on the following criteria:

- At high risk for rapidly progressive disease as evidenced by:
  - Positive serum RF or at least three erosions present on x-rays of the hands/ wrists, and forefeet
  - ≥ 10 swollen joints and ≥ 12 tender/painful joints
  - Either elevated acute phase reactant (ESR ≥ 28 mm/hr or CRP ≥ 2.0 mg/dL) or duration of morning stiffness ≥ 45 minutes

Other eligibility criteria were:

- At least 18 years of age
- Fulfilled the 1987 American Rheumatism Association criteria for active RA
- Functional Class I, II, or III by the ACR revised classification
- Early RA, defined as duration of disease ≤ 3 years from time of diagnosis.
- No prior therapeutic treatment with MTX for any medical condition
- Prior treatment with a DMARD other than MTX was permitted. All DMARDs were washed out for a minimum of 1 month before administration of study drug.
- Nonsteroidal anti-inflammatory therapy and prednisone (≤10 mg daily) were allowed provided the doses were stable for at least 4 weeks before the study and remained stable during the first 6 months of the study
- ALT or AST ≤ 1.5 x laboratory's upper limit of normal; hemoglobin stable at ≥ 8.5 g/dL; platelet count ≥125,000/cmm; white blood cell count ≥ 3,500 cells/cmm; and serum creatinine < 2 mg/dL

2.3 Dose of Study Medications

SC Study Medication: All patients received 10 or 25 mg Enbrel or placebo twice weekly by SC injection.

PO Study Medication: All patients received oral placebo tablets or oral MTX weekly. The initial dose of 3 tablets (7.5 mg MTX) was increased to 6 tablets (15 mg) at week 4 and to 8 tablets (20 mg) at week 8 if the patient had any active joints. This rapid dose escalation was chosen to ensure the maximum efficacy of MTX. One 5-mg reduction in oral dose was allowed for patients whose liver transaminase levels were elevated to Grade

2 (or greater) toxicity or if the patient had adverse events that could be due to or exacerbated by MTX. All patients received folic acid (1 mg per day).

2.4 Study Evaluations

Radiographs of the hands/wrists and forefeet were obtained at baseline, 6 months, and 12 months. For RF negative patients, the screening film taken to establish eligibility could be used as the baseline film provided it was acquired within 1 month of the first dose of study drug. Clinical and laboratory measures were assessed at screening, baseline, week 2, and months 1-6, 8, 10, and 12. Clinical disease activity measures included evaluation of 71 joints for tenderness and 68 joints for swelling, physician's and patient's global assessments of disease, patient's assessment of pain (visual analog scale), patient's assessment of disability (Health Assessment Questionnaire), ESR, and CRP level. Patients who discontinued study drug for any reason were to continue study evaluations for 12 months.

3.0 Methods

The efficacy endpoints for this trial were all within the first 12 months. The second year of the trial, during which safety and radiographic data continue to be acquired, is ongoing.

3.1 Primary Endpoint for Prevention of Structural Damage

3.1.1 Equivalence Endpoint

The primary radiographic endpoint was to compare the progression of joint damage between the Enbrel 25 mg and MTX groups over 12 months using TSS.

3.1.2 Superiority Endpoint

The primary radiographic endpoint specified in the original protocol was to compare progression of joint damage among the 3 treatment groups over 12 months using Sharp erosion score.

3.2 Primary Endpoint for Improvement in Signs and Symptoms of RA

The primary clinical endpoint was to compare disease activity among the 3 treatment groups over 6 months using a cumulative index (ACR-N AUC) derived from the ACR definition of improvement in RA.

3.3 Other Clinical Endpoints

- ACR Responses
- Individual Arthritis Activity Measures
- Major Clinical Response
- Health-Related Quality of Life
- Prevention of Disability

3.4 Statistical Analyses

3.4.1 Prevention of Structural Damage

The ERA trial began on May 13, 1997. With regard to the primary radiographic endpoint, the trial was originally designed, sized, and conducted as a superiority trial. The original radiographic endpoint was superiority in change in Sharp erosion score over 12 months. After all patients had been accrued and randomized, but prior to study completion and unblinding, the protocol was amended to change the primary structural damage endpoint to non-inferiority of Enbrel 25 mg to MTX with respect to TSS at 12 months. The primary endpoint was changed because data became available from 2 large active-controlled trials studying leflunomide (Strand 1999; Schiff 1999). These trials clearly demonstrated that MTX prevented structural damage as measured by TSS. Since MTX is considered by most rheumatologists to be the "gold standard" DMARD and with solid evidence demonstrating that MTX prevents radiographic damage, it became important to establish equivalence to MTX. The amendment did not change the conduct of the study; only the analysis plan was modified. The results of both of these analyses are presented in this summary.

Radiographs of the hands/wrists and feet of each patient were obtained at baseline and 6 and 12 months. Digitized images of each radiograph were scored by 2 of 6 physicians (5 radiologists and 1 rheumatologist) who were trained in the Sharp method. Each physician read approximately the same number of films with every other physician. Thus there were 15 blocks of approximately 42 patient sets of films, with each block scored by a different combination of 2 readers. The mean score from the 2 readers was used in the analysis. The assessors were blinded to study treatment and the chronological order of the images.

<u>Sharp Method</u>

The Sharp method was used for evaluating the degree of structural damage in patients with RA (Sharp 1971; Sharp 1985; van der Heijde 1989; Sharp 1995). Seventeen joints of each hand/wrist and 6 joints of each forefoot were scored for erosions on a scale from

0 – 5 (0 = no damage); the scores from each joint were summed to determine erosion score (maximum erosion score = 230). Sixteen joints of each hand/wrist and the 5 metatarsophalangeal (MTP) joints of each forefoot were scored for JSN on a scale from 0 – 4 (0 = no damage); the scores from each joint were summed to determine JSN score (maximum JSN score = 168). Erosion score and JSN score were added to determine the total Sharp score (maximum total score = 398).

Equivalence Endpoint

The equivalence endpoint compared the change from baseline in TSS at 12 months for MTX and Enbrel 25 mg. According to FDA guidelines for RA therapeutics, equivalence trials should be designed to demonstrate that the test drug is adequately similar to an active control using a predefined equivalence test (FDA 1999). The protocol must declare the magnitude of difference between test drug and active control that will be considered clinically insignificant. This value becomes the allowable difference between the 2 agents. As described in the Introduction (Section 1.4), the rate of progression in TSS in untreated patients was predicted to be 6 units per year and the rate of progression in the MTX group was predicted to be 2 units per year. Thus the expected MTX benefit is the difference between these, or 4 total Sharp units/year. The definition of equivalence for this trial specified that Enbrel must preserve at least 70% of the predicted benefit of MTX, as illustrated in the following figure.

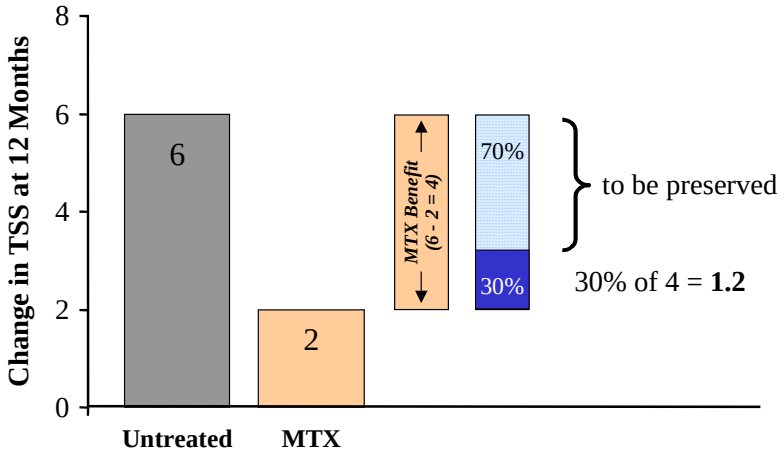


Figure 3.4.1A Equivalence Criterion for Enbrel 25 mg and MTX

In order for Enbrel to be equivalent to MTX, the upper limit of the 95% confidence interval for the difference in TSS between Enbrel and MTX at 12 months had to be less than 1.2 units, which would preserve 70% of the 4 units difference predicted between untreated and MTX-treated patients. This confidence interval and the analysis plan were discussed with the FDA.

The primary analysis was performed using a random coefficients regression model. This model fit an intercept and slope for each patient's damage score over time. Treatment effect, duration of disease stratum, and reader pair were included as terms in the model. The model assumed that the data would be normally distributed.

Patients who completed at least 12 months of evaluations but who discontinued study drug prior to the 12-month evaluation had outcome measures analyzed as part of the treatment group to which they were randomized. Patients who discontinued study drug or dropped out of the study had an additional radiographic evaluation performed at the point of dropout when possible. All patients were included in an analysis of radiographic endpoints, which described progression for subjects who continued on study treatment as well as those who discontinued.

Superiority Endpoint

The superiority endpoint compared the change from baseline in Sharp erosion score at 12 months. For this analysis, actual change scores (no statistical modeling) were compared. For patients who had a missing film, a linear extrapolation was used. The extrapolation considers the first and last observations, adjusted over time.

Rank tests stratified by duration of disease (Van Elteren tests) were used to compare the three treatment groups with respect to the radiographic superiority endpoint.

Missing Data

Subjects with a single film were included in the analysis by assigning scores as follows: subjects with no follow-up film (n = 15) were assigned the highest score observed at 12

months among subjects with the same baseline score. One patient had no films and was excluded from the radiographic analyses.

3.4.2 Signs and Symptoms Endpoint

ACR-N AUC

The FDA Guidance Document for clinical development of RA therapeutics outlines the advantage of using cumulative measures of disease activity that consider patient response throughout the study rather than only at the final visit (FDA 1999). The primary clinical endpoint was to compare disease activity among the 3 treatment groups over 6 months using a cumulative index (ACR-N AUC) derived from the ACR definition of improvement in RA.

ACR-N uses the same criteria as the ACR 20. It gives a precise value reflecting a patient's response at a specific time point. ACR-N is calculated by taking the lowest percent improvement in (1) swollen joint count, (2) tender joint count, and (3) the median of the remaining 5 components of the ACR response: (1) patient's assessment of pain, (2) patient's global assessment of disease activity, (3) physician's global assessment of disease activity, (4) patient's assessment of physical function, and (5) acute-phase reactant value – ESR or CRP. The calculation and interpretation of ACR-N is illustrated in the following figure.

	% Improvement	
Criteria	Patient #1	Patient #2
Swollen-joint count	28%	48% ←
Tender-joint count	21% ←	55%
MD global assessment	40%	52%
Pt global assessment	35% (median)	51%
VAS for pain	26%	49% (median)
HAQ	22%	22%
CRP or ESR	47%	47%
ACR20	*Yes* ←	*Yes* ←
ACR50	No	No
ACR70	No	No
ACR-N	*21%* ←	*48%* ←

Figure 3.4.2A Calculation of Numeric ACR (ACR-N)

In this example, Patient #2 shows substantially more improvement than Patient #1. Neither ACR 20 nor ACR 50 criteria would distinguish these patients. Both are ACR 20 responders. However, Patient #2 approaches achieving an ACR 50 response. By determining the ACR-N of each patient, the better response of Patient #2 can be quantified.

ACR-N was evaluated for each patient at week 2 and months 1, 2, 3, 4, 5, and 6 for a total of 7 possible observations over six months. The ACR-N AUC is the area under the curve for ACR-N at each evaluation plotted over time. Ranked values of ACR-N AUC were analyzed using ANOVA with factors of treatment, disease duration group, and their interaction.

3.4.3 Other Endpoints

ACR Responses

The ACR 20 response is defined as at least 20% improvement in tender joint count and swollen joint count plus ≥ 20% improvement in at least 3 of the 5 remaining ACR criteria

described above. The ACR 50 and ACR 70 response levels are calculated in an analogous fashion.

Chi-square tests were used to compare the treatment groups with respect to ACR response rates (20%, 50%, 70%) at individual time points. The Cochran Mantel-Haenszel test was used to compare treatments with respect to the frequency with which patients met ACR 20, ACR 50, and ACR 70 criteria. The area under the curve of ACR responders (weeks at ACR response) was also calculated both over 6 months and over 12 months.

Individual Arthritis Activity Measures

ACR component variables were also analyzed at individual time points as percent change from baseline using the same ANOVA as for ACR-N AUC. Percent change from baseline in duration of morning stiffness, which is not normally distributed, was tested using the non-parametric Kruskal-Wallis test.

Major Clinical Response

Major clinical response is defined as maintenance of a 70% ACR response over a continuous 6-month period (FDA 1999). To satisfy the criteria, every evaluation must indicate $\geq$ 70% improvement during a 6-month observation period. In order to achieve a major clinical response in one year, patients must have achieved an ACR 70 by Month 6. ACR response rates were compared using Fisher's exact test.

Health-Related Quality of Life

The SF-36 is a 36-item questionnaire that has been used to assess health status in a number of patient populations. It includes 8 separate subscales or domains: physical functioning; role limitations attributable to physical problems; role limitations attributable to emotional problems; social functioning; general health; vitality; bodily pain; and mental health. The eight scales range from 0 (worst) to 100 (best) and have a mean of 50 units and a standard deviation of 10 units in the general US population. All scores above

50 can be interpreted as better than the general population norm and all scores below 50 can be interpreted as worse than the general population norm.

The SF-36 data are commonly displayed as 2 summary scales: the physical component summary (PCS) and the mental component summary (MCS). All 8 subscales are incorporated into both the PCS and MCS but are weighted differently. Physical functioning, role physical, and bodily pain contribute most heavily to scoring the PCS. The mental health, role emotional, and social functioning scales contribute most to scoring the MCS. The PCS and MCS scales also have a mean of 50 units and a standard deviation of 10 units in the general US population.

Change from baseline at 12 months was computed for PCS, MCS, and the 8 scales of the SF-36. If an SF-36 score was missing at 12 months, the following convention was applied. Patients were divided into cohorts determined by their baseline score. (The 100-point scales were divided into 50 2-unit intervals.) The worst 12-month score observed in the patient's baseline cohort was substituted for the missing score. The changes were analyzed using the ANOVA model described above for ACR-N AUC.

Prevention of Disability

The HAQ is the most commonly used arthritis-specific quality of life instrument. The HAQ is generally used for calculation of the disability index, which assesses the patient's functional ability. The disability index is composed of eight categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). Each category has at least two questions and is scored from 0 (best) to 3 (worst).

Prevention of disability was analyzed using the HAQ disability index over 12 months. The total change in score for the HAQ (over time as AUC) was computed and compared between treatments using the same ANOVA as for the ACR-N AUC.

3.5 Safety Endpoints

All patients who received at least one dose of study drug were evaluated for safety. The evaluations included: vital signs, physical examinations, hematology and chemistry profiles, urinalysis with microscopic analysis, symptoms and toxicity assessments, adverse events and serious adverse events (SAEs), premature discontinuations, and deaths on study or within 30 days of the last dose of study drug.

Adverse Events

The types and intensities (grades) of noninfectious AEs, infections, and injection site reactions (ISRs) occurring on or after the first dose date were tabulated. Adverse events were coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary to classify events by preferred term and body system. For each patient, the most severe intensity of all occurrences of an event (within a body system, where appropriate) was recorded. Intensities were determined using modified National Cancer Institute (NCI) Common Toxicity Criteria. Patients may have more than one type of event within the same body system or within several body systems.

Serious Adverse Events

The Code of Federal Regulations defines an event as serious if it results in death, is life-threatening, results in persistent or significant disability, results in drug dependency or abuse, requires inpatient hospitalization or prolonged hospitalization, is a congenital anomaly, or is a symptomatic overdose. A serious adverse event (SAE) also includes any important medical event that jeopardizes the patient or requires medical or surgical intervention to prevent one of the outcomes listed.

Infections and Injection Site Reactions (ISRs)

For this study, infections and injection site reactions were recorded on individual forms and compiled separately from other adverse events. Infection intensity was graded as follows: Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening. NCI Common Toxicity Criteria were used to define the grade of ISRs, as

follows: Grade 1 = erythema; Grade 2 = pain, swelling, pruritus, phlebitis with or without erythema; Grade 3 = ulceration; and Grade 4 = plastic surgery required.

Laboratory

Laboratory abnormalities and toxicities from all samples collected after the first dose of study drug were summarized for safety. Baseline samples for laboratory tests were generally collected on Day 1, immediately before the first dose of study drug. Results were evaluated by grade according to the NCI Common Toxicity criteria (Ajani 1990); by low, high, and last change from baseline value; and by shifts in and out of normal laboratory ranges.

Antibody to Enbrel

Serum samples were analyzed for the presence of antibody to Enbrel using a validated modification of a published ELISA assay (Moreland 1997). To increase the sensitivity of the enzyme-linked immunoabsorbent assay (ELISA), the plate-coating concentration of Enbrel was increased from 63 mg/mL to 250 mg/mL. Samples that were positive in the ELISA were tested for the presence of neutralizing antibodies to Enbrel. Neutralizing antibodies are those that interfere with the binding of TNF to the receptor portion of Enbrel.

Analyses

Proportions of patients with events were compared overall and pairwise using Fisher's exact test. Event rates (per patient-year) were compared using pairwise exact binomial tests. All tests were 2-sided.

4.0 Study Population

4.1 Patient Disposition

A total of 632 patients received at least one dose of active study drug: 217 patients in the MTX group, 208 patients in the Enbrel 10 mg group, and 207 patients in the Enbrel 25 mg group. Safety analyses and efficacy analyses included all 632 patients who received at least one dose of study drug. One patient in the Enbrel 25 mg group had no x-rays and was omitted from the radiographic analyses.

The following table describes the study completion status at the end of the 12-month dosing period.

Table 4.1A Study Completion Status at 12 Months

(Percent of Patients)

	MTX	Enbrel	
Status	**N = 217**	**10 mg N = 208**	**25 mg N = 207**
Completed study evaluations:	93%	90%	93%
On study drug	79%	80%	85%
Off study drug	14%	11%	8%
Discontinued study (no 12 month evaluation)	7%	10%	7%

Most patients completed 52 weeks of dosing. Of the patients who discontinued study drug, most remained in the study for evaluations. Overall, 14% of patients in the MTX group, 11% in the Enbrel 10 mg group, and 8% in the Enbrel 25 mg group discontinued study drug but remained in the study for evaluations. These patients were treated for RA as prescribed by their physician.

The reasons patients discontinued study drug are summarized in the following table.

Table 4.1B Reasons for Discontinuing Study Drug

(Percent of Patients)

	MTX	Enbrel	
		10 mg	25 mg
Adverse Event*	10%	4%	5%
Lack of Efficacy	4%	7%	5%
Other	7%	9%	5%

* p = 0.016, MTX vs all Enbrel

Significantly more MTX-treated patients than Enbrel patients discontinued study drug due to AEs: 10% in the MTX group, compared to 4% in the Enbrel 10 mg group and 5% in the Enbrel 25 mg group (p = 0.016, MTX vs all Enbrel). In addition, significantly more MTX patients had oral study drug dose reduction due to AEs: 15% in the MTX group compared to 4% in the Enbrel 10 mg and 2% in the Enbrel 25 mg groups (p < 0.001, MTX vs all Enbrel).

4.2 Demographics and Disease History

Demographic characteristics and the disease history of patients who received study drug are shown in the following table.

Table 4.2A Demographics and Treatment

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Age:			
Mean age (years)	49	50	51
Range (years)	21-80	19-84	21-82
≥65 years (%)	15	14	18
Female (%)	75	75	74
Race:			
Caucasian (%)	88	84	86
Hispanic (%)	4	8	5
African-American (%)	6	5	4
Other (%)	2	3	5
Mean weight (kg)	76	78	79
RA duration (years):			
Mean	1	0.9	1
Median	0.7	0.6	0.7
<18 months (%)	75	76	76
18-36 months (%)	25	24	24
DMARD treatment:			
Any prior (%)	46	39	40
Mean no.	0.6	0.5	0.5
Concomitant therapy at baseline (%)			
NSAIDs	80	76	86
Corticosteroids ≤ 10 mg/day	41	42	39

The 3 treatment groups were well balanced with regard to all demographic variables. Of the 632 patients in this study, 59% had never received a DMARD. At the screening visit, 24% were receiving a DMARD and required a 4-week washout period. Most patients receiving a DMARD at the screening visit were receiving hydroxychloroquine (17% of all patients) or sulfasalazine (7% of all patients). Few patients (<1%) were receiving oral or injectable gold or azathioprine. Patients who had prior MTX were excluded from the study.

The patients enrolled in this trial had risk factors for rapidly progressive disease as shown in the following table.

Table 4.2B Risk Factors for Progressive Disease

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Swollen Joint Count (mean)*	24	24	24
RF positive (% of patients)	89%	88%	87%
Erosions at baseline (% of patients)	87%	85%	88%
Elevated ESR†			
Elevated ESR (% of patients)	63%	61%	62%
Mean value (mm/hr)	40	41	38
Elevated CRP‡			
Elevated CRP (% of patients)	76%	78%	79%
Mean value (mg/dL)	3.7	4.4	3.3

* Scale 0-68
† > 13 mm/hr for men and > 30 mm/hr for women
‡ > 0.79 mg/dL

The study population was enriched for patients who were likely to have progression of joint damage. Though the patients in this study were within 3 years of diagnosis, they had highly active disease.

Other baseline disease activity measures are shown in the following table.

Table 4.2C Mean Baseline Arthritis Activity

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Tender joint count*	30	31	31
MD global assessment**	6.0	6.3	6.2
Pt. global assessment**	6.1	6.1	6.1
Pain (VAS)**	5.6	5.6	5.9
Disability (HAQ)†	1.4	1.4	1.5
AM stiffness (hr)	3.7	3.7	3.8
SF-36‡			
PCS#	29	28	28
MCS§	47	47	46

* Scale 0 - 71
** 0 = best, 10 = worst
† 0 = best, 3 = worst
‡ SF-36 (normalized; 0 = worst, 100 = best. Mean for normal population is 50 units). N's for this measure were 215, 208, and 205 for MTX, Enbrel 10 mg, and Enbrel 25 mg groups respectively. Two MTX patients and two 25 mg patients had missing evaluations at baseline.
# Physical component summary of SF-36 (0 = worst, 100 = best; 50 = US norm)
§ Mental component summary of SF-36 (0 = worst, 100 = best; 50 = US norm)

The disease activity measures were balanced among the three treatment groups at baseline.

Patients had baseline radiographs of hands/wrists and forefeet taken on or before Day 1. Baseline radiographic features are summarized in the following table.

Table 4.2D Baseline Radiographic Features

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 206
Total Sharp score			
Mean	12.9	11.2	12.4
Median	8.5	6.0	6.8
Range	0-77	0-100	0-113
Erosion score			
Mean	7.5	6.1	6.4
Median	3.5	3.0	3.0
Range	0-45	0-72	0-69
JSN score			
Mean	5.4	5.0	6.0
Median	3.5	2.0	3.5
Range	0-36	0-44	0-48

The treatment groups were well balanced with respect to baseline radiographic features. The mean TSS at baseline was 12.9 for patients in the MTX group, 11.2 for patients in the Enbrel 10 mg group, and 12.4 for patients in the Enbrel 25 mg group. Patients in all 3 treatment groups were experiencing rapid progression of disease at baseline.

5.0 Compliance

5.1 Subcutaneous Study Drug Administration

In this trial, all patients received one active treatment (MTX or Enbrel) and one placebo (oral or SC). Compliance with SC dosing was high and the majority of patients missed no doses of SC study drug. Subcutaneous study drug administration is summarized in the following table.

Table 5.1A Subcutaneous Study Drug Dosing Summary

	SC Placebo*	Enbrel	
	N = 217	10 mg N = 208	25 mg N = 207
Pts. with no missed doses	70%	75%	70%
Pts. with missed doses:			
1	9%	9%	13%
2 - 3	10%	8%	11%
≥ 4	12%	8%	6%

* patients also received oral MTX

5.2 Oral Study Drug Administration

In order to provide optimal performance of oral MTX, the dose was rapidly escalated. All patients started the study at a dose of 7.5 mg MTX (or 3 placebo tablets). At week 4 the dose was escalated to 15 mg MTX (or 6 placebo tablets) and at week 8 the dose was escalated to 20 mg/week (or 8 placebo tablets). The escalation of oral study drug is shown in the following figure.

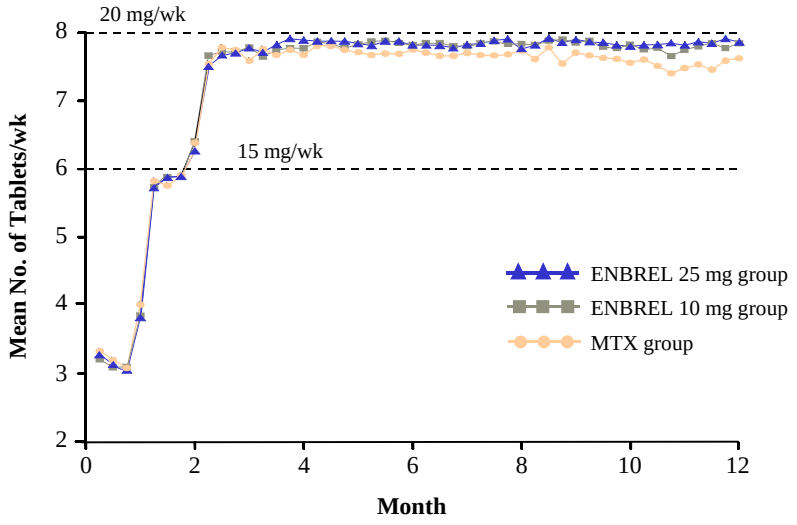


Figure 5.2A Escalation of Oral Study Drug (MTX or Placebo)

The mean dose for patients in the MTX group after dose escalation was complete was 19 mg/week (median MTX dose was 20 mg/week). In the MTX group, the percent of patients who were maintained at the highest permissible dose declined slightly over time on study. In the MTX group 15% of patients had their dose reduced, compared to 4% in the Enbrel 10 mg group and 2% in the Enbrel 25 mg group ($p < 0.001$, MTX vs all Enbrel and $p < 0.001$, MTX vs Enbrel 25 mg). Reductions in the MTX dose were primarily due to adverse events (8%) or elevated liver function tests (7%).

5.3 X-ray Acquisition

In this study, compliance with x-ray acquisition was high: 98% of patients had at least 2 x-rays and 92% of patients had 3 or more x-rays. Fifteen patients had only a baseline x-ray (4 patients in the MTX group, 9 in the Enbrel 10 mg group, and 2 in the Enbrel 25 mg group). Per protocol, radiographs acquisition could fall within 30 days of the actual time point (baseline, 6 months, and 12 months). The vast majority of patients had films taken per protocol-specified time points, as presented in the following figure.

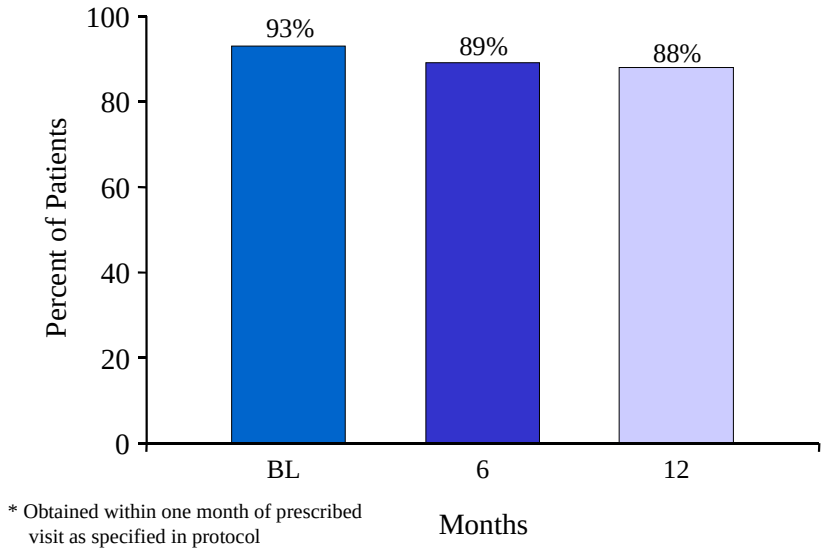


Figure 5.3A Complicance with Protocol-Specified Time Points for Radiographs

6.0 Efficacy - Prevention of Structural Damage Endpoint

6.1 Equivalence Endpoint

The primary radiographic endpoint for the equivalence analysis was to compare radiographic progression in the Enbrel 25 mg and MTX groups to demonstrate that Enbrel was at least equivalent to MTX in preventing damage. The 95% one-sided confidence interval for difference in change in TSS per year between the Enbrel 25 mg and MTX groups could not be greater than 1.2 units and was analyzed by the random coefficients model.

The mean changes from baseline in TSS at 12 months for the 3 treatment groups are presented in the following figure.

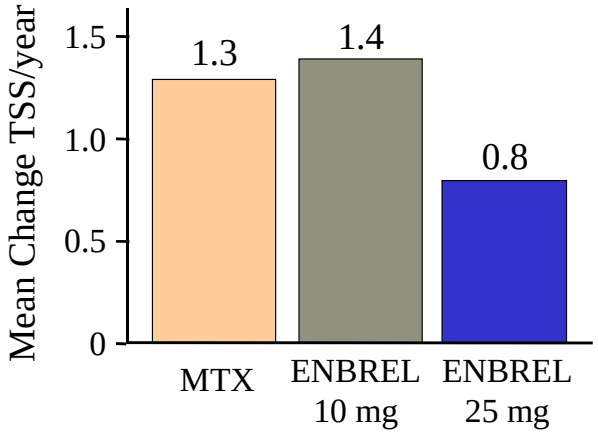


Figure 6.1A Change in Total Sharp Score over 12 Months: Equivalence Endpoint

The primary radiographic endpoint was achieved; Enbrel slowed radiographic progression in patients with RA, with 25 mg being at least equivalent to MTX. The mean progression for patients receiving 25 mg Enbrel was 0.8 units/year, compared to 1.3 units/year for patients receiving MTX. The difference between the progression rates of Enbrel 25 mg and MTX was -0.53, with the upper bound of the 1-sided 95% (2-sided 90%) CI of 0.16. This is well within the threshold prospectively defined to establish that Enbrel and MTX

are at least equivalent (1.2 total Sharp score units/year). Enbrel 25 mg is estimated to have 113% of the predicted MTX benefit and with one-sided 95% confidence it preserves at least 96% of the predicted MTX benefit. Another perspective indicating the robustness of the results is that the equivalence criterion would have been met even if the MTX to placebo effect used was only 0.23 Sharp units.

6.2 Superiority Endpoint

The original primary endpoint of superiority in change in erosion score over 12 months was also achieved. This was analyzed using actual (raw) change scores, with no statistical modeling. There was a statistically significant difference among the 3 treatment groups as shown in the following figure.

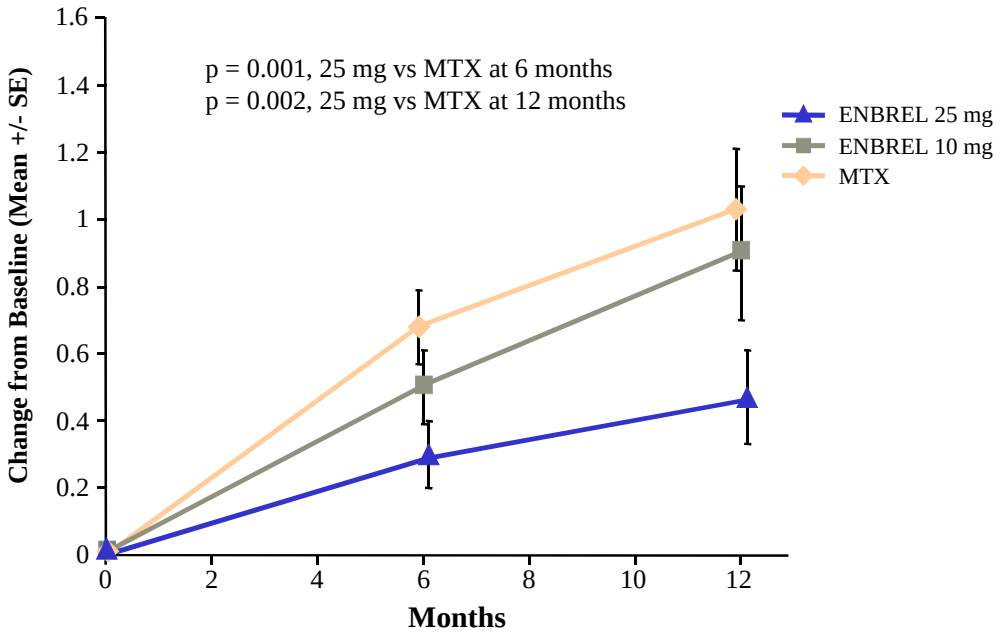


Figure 6.2A Change in Erosion Score over 12 Months: Superiority Endpoint

Enbrel 25 mg was significantly better than MTX in preventing erosions. The mean change from baseline in erosion score at month 12 for MTX patients was 1.03 units, compared to 0.90 units in Enbrel 10 mg patients and 0.47 units in Enbrel 25 mg patients

(overall p = 0.005; pairwise Enbrel 25 mg vs MTX, p = 0.002). These differences were robust and were confirmed by multiple sensitivity analyses.

6.3 Prevention of New Erosions

Patients in the study were also evaluated to determine whether their erosion score increased over time (protocol-defined endpoint). The proportion of patients who had no change in erosion score was analyzed. These data were quite robust and were confirmed in multiple sensitivity analyses.

Table 6.3A Percent of Patients With No Progression* of Erosions at 12 Months

	MTX	Enbrel		Enbrel 25 mg vs MTX p-value
	N = 217	10 mg N = 208	25 mg N = 206	
Model	57%	63%	75%	0.001
Actual Scores	60%	66%	72%	0.007

* No progression defined as less than 0.5 units change

Significantly fewer patients in the Enbrel 25 mg group than in the MTX group had progression of erosion scores at 12 months: 75% in the Enbrel 25 mg group compared with 57% in the MTX group (p = 0.001).

6.4 Effects on Total Sharp Score

The change in TSS at month 12 was also analyzed. Results are summarized in the following figure.

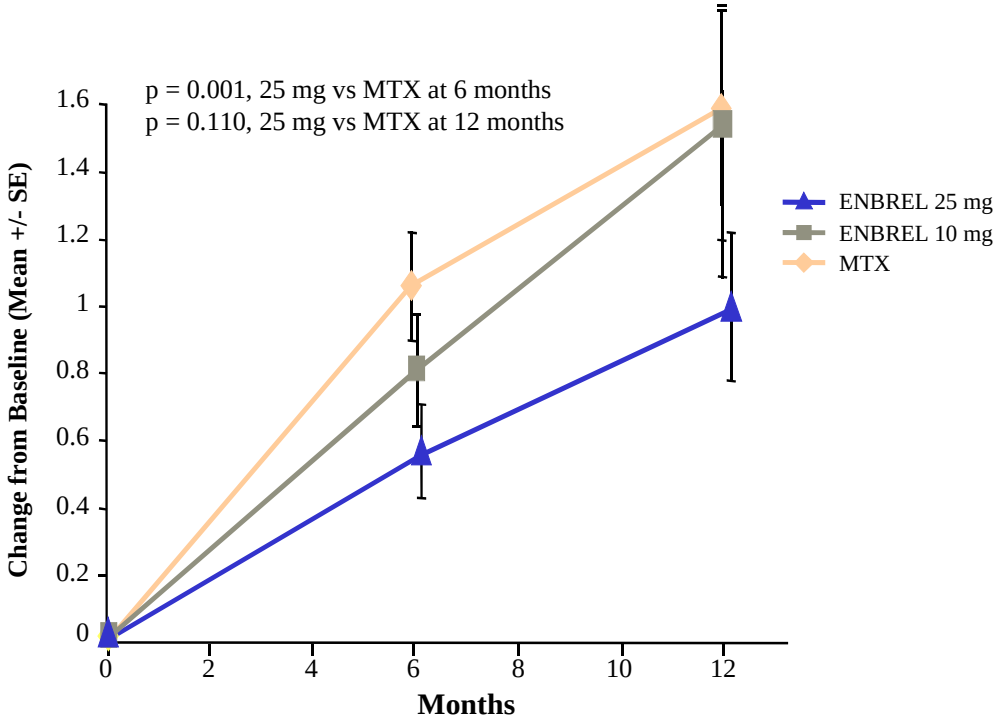


Figure 6.4A Change in Total Sharp Scores at Month 12

With respect to change in total Sharp score, Enbrel 25 mg was significantly better than MTX at month 6, with a trend toward superiority at month 12. Consistent with the change in erosion score and total Sharp score, greater numbers of patients treated with 25 mg Enbrel had no radiographic progression at month 12, as shown in the following table.

Table 6.4A Percent of Patients With No Progression* of Total Sharp Score at 12 Months

	MTX	Enbrel		Enbrel 25 mg vs MTX p-value
	N = 217	10 mg N = 208	25 mg N = 206	
Model	50%	54%	62%	0.014
Actual Scores	56%	62%	62%	0.219

* No progression defined as less than 0.5 units change

6.5 Effects on Joint Space Narrowing

JSN was not different in the MTX group compared to the Enbrel groups in any of the analyses. The 3 treatment groups showed similar low rates of progression of JSN. Results are illustrated in the following figure.

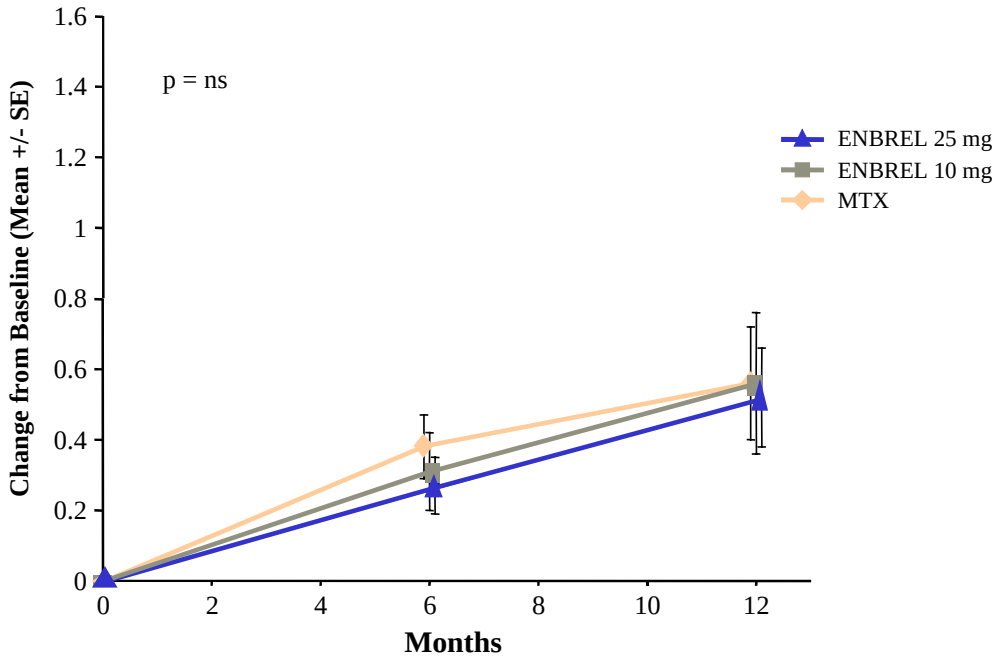


Figure 6.5A Change in JSN Scores at Month 12

6.6 Rapidity of Response

The onset of DMARD effect was examined by comparing the rate of progression during the first 6 months of the study with the rate during the second 6 months. Consistent with other studies (Rau 1998), there was a slower rate of progression within the MTX group during months 6-12 compared to months 1-6 ($p < 0.001$ for change in erosion score, $p = 0.005$ for change in TSS). In the Enbrel 25 mg group, the rate of progression during months 1-6 was significantly less than the rate in the MTX group over that same time period ($p = 0.001$ for both change in TSS and change in erosion score). However, within the Enbrel 25 mg group, there were no differences when the rate during months 1-6 was

compared to months 6-12. The low rate of progression was constant over the full 12 months.

6.7 Patient Subsets

Efficacy of 25 mg Enbrel in preventing erosions compared to MTX was analyzed in subsets of the overall population. As with most subset analyses, the sample sizes of some of the subgroups were small. Nevertheless, when analyses were performed by gender, age, ethnicity, disease duration, baseline disease activity (number of active joints, ESR, CRP, RF status), baseline radiographic damage, DMARD withdrawal, and concomitant therapy (NSAID, corticosteroid use), the majority of subgroups showed benefit of Enbrel in prevention of erosions compared to MTX (odds ratio greater than 1).

7.0 Efficacy - Signs and Symptoms

7.1 Primary Endpoint: ACR N-AUC over 6 Months

The primary clinical endpoint in this study was to compare disease activity as measured by the ACR-N AUC among the 3 treatment groups over 6 months. This endpoint was achieved. These data and supportive data at 3-month intervals are shown below.

Table 7.1.A Mean ACR-N AUC* over 12 Months

	MTX	Enbrel		
Baseline to:	**N = 217**	**10 mg N = 208**	**25 mg N = 207**	**Enbrel 25 mg vs MTX p value**
Month 3	3.9	5.4†	6.2	< 0.001
Month 6 Primary Endpoint	**11.5**	**13.0**	**15.3**	**0.002**
Month 9	20.1	21.1	25.2	0.004
Month 12	28.7	28.5	34.9††	0.009

* Units are ACR-N•years
† $p < 0.05$, Enbrel 10 mg vs MTX
†† $p < 0.05$, Enbrel 10 mg vs Enbrel 25 mg
p values determined by ANOVA

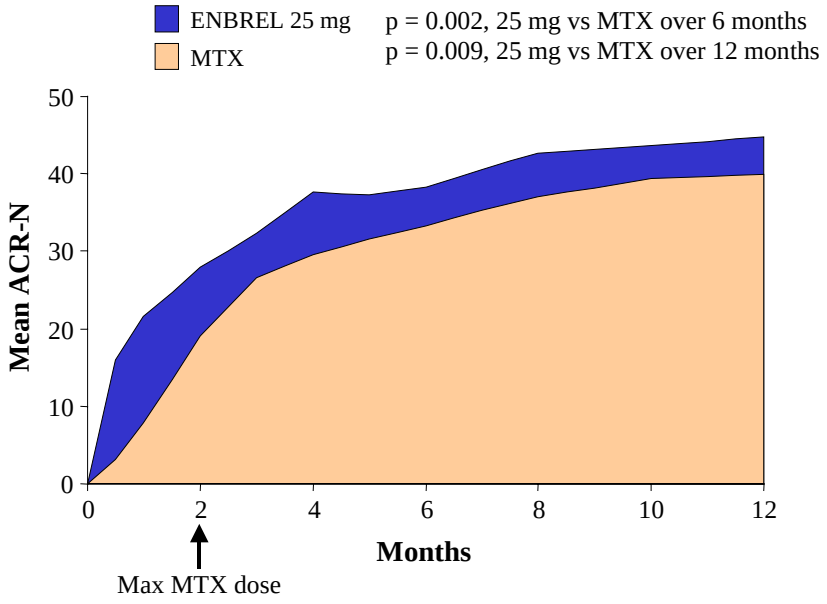


Figure 7.1A AUC for ACR-N Over 12 Months: Primary Clinical Endpoint

There was an overall statistically significant difference among the 3 treatment groups in ACR-N AUC at month 6 (p = 0.006). Compared to MTX, the Enbrel 25 mg group had a more rapid effect and achieved significantly greater ACR-N AUC over 6 months (p = 0.002) and over 12 months (p = 0.009). The Enbrel 10 mg group had less improvement than the Enbrel 25 mg group.

7.2 Supportive Clinical Efficacy

7.2.1 ACR Response

The proportion of patients meeting the ACR 20, ACR 50, and ACR 70 responses were compared among the treatment groups. The results for the Enbrel 25 mg and MTX groups are summarized in the following figure. The 10 mg dose of Enbrel was always less effective than the 25 mg dose.

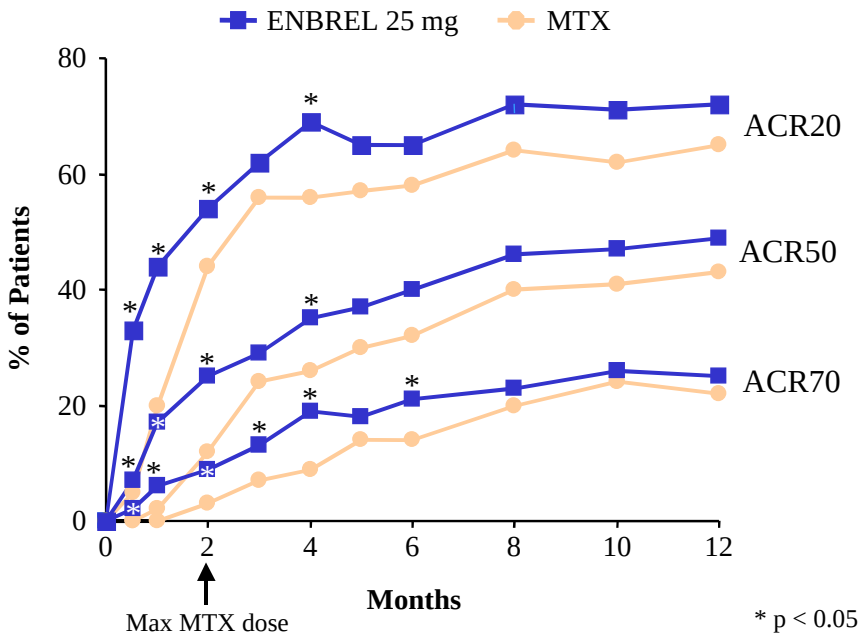


Figure 7.2.1A ACR Responses

Consistent with a more rapid onset of treatment effect with Enbrel, patients in the Enbrel 25 mg group improved more rapidly than patients on MTX. Significantly greater proportions of patients in the Enbrel 25 mg group than in the MTX group achieved ACR 20, ACR 50, and ACR 70 responses within the first 6 months of treatment. In the second half of the study, MTX and 25 mg Enbrel had similar responses. However, at every evaluation, the largest number of patients achieving ACR 20, ACR 50, and ACR 70 responses were seen in the Enbrel 25 mg group.

7.2.2 Major Clinical Response

Major clinical response in patients with RA is defined as maintenance of an ACR 70 response over a continuous six-month period (FDA 1999). To satisfy the criteria, every evaluation must indicate $\geq$ 70% improvement during a 6 month observation period. To achieve this during the 1-year trial, a patient must have reached an ACR 70 response by month 6. The major clinical response rates among the three treatment groups are summarized in the following table.

Table 7.2.2A Major Clinical Response

	MTX	**Enbrel**	
	N = 217 n (%)	**10 mg N = 208 n (%)**	**25 mg N = 207 n (%)**
Patients who achieved major clinical response	18 (8)	10 (5)	23 (11)†

† p <0.02, Enbrel 10 vs Enbrel 25 mg
p values determined by Fisher's exact test

Major clinical responses were attained in this trial, with a clear Enbrel dose response observed (Enbrel 25 mg vs 10 mg, $p < 0.019$).

The percent of patients in the Enbrel 25 mg group who achieved an ACR 70 response continued to increase at each visit up until month 10 (see Figure 7.2.1A). The number of patients who achieved an ACR 70 response at any time during the study was also calculated and is presented in the following table.

Table 7.2.2B Percent of Patients With ACR 70 Responses

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Patients who achieved ACR 70 by:			
Month 3	7%	10%	19%*
Month 6	20%	25%	31%*
Month 12	35%	34%	40%

*p <0.01, Enbrel 25 mg vs MTX
p values determined by chi-square test

By month 12, 40% of patients in the Enbrel 25 mg group had achieved an ACR 70 response during at least 1 visit.

7.2.3 Individual Arthritis Activity Measures

Improvements in the individual measures of arthritis activity were also analyzed. The mean (or median) changes from baseline were calculated for the following parameters: total swollen joint count; total tender/painful joint count; pain as quantified by the patient VAS; patient global assessment of disease status; physician global assessment of disease status; duration of morning stiffness; ESR; and CRP. The comparisons between Enbrel 25 mg and MTX for representative parameters are shown in the following figure.

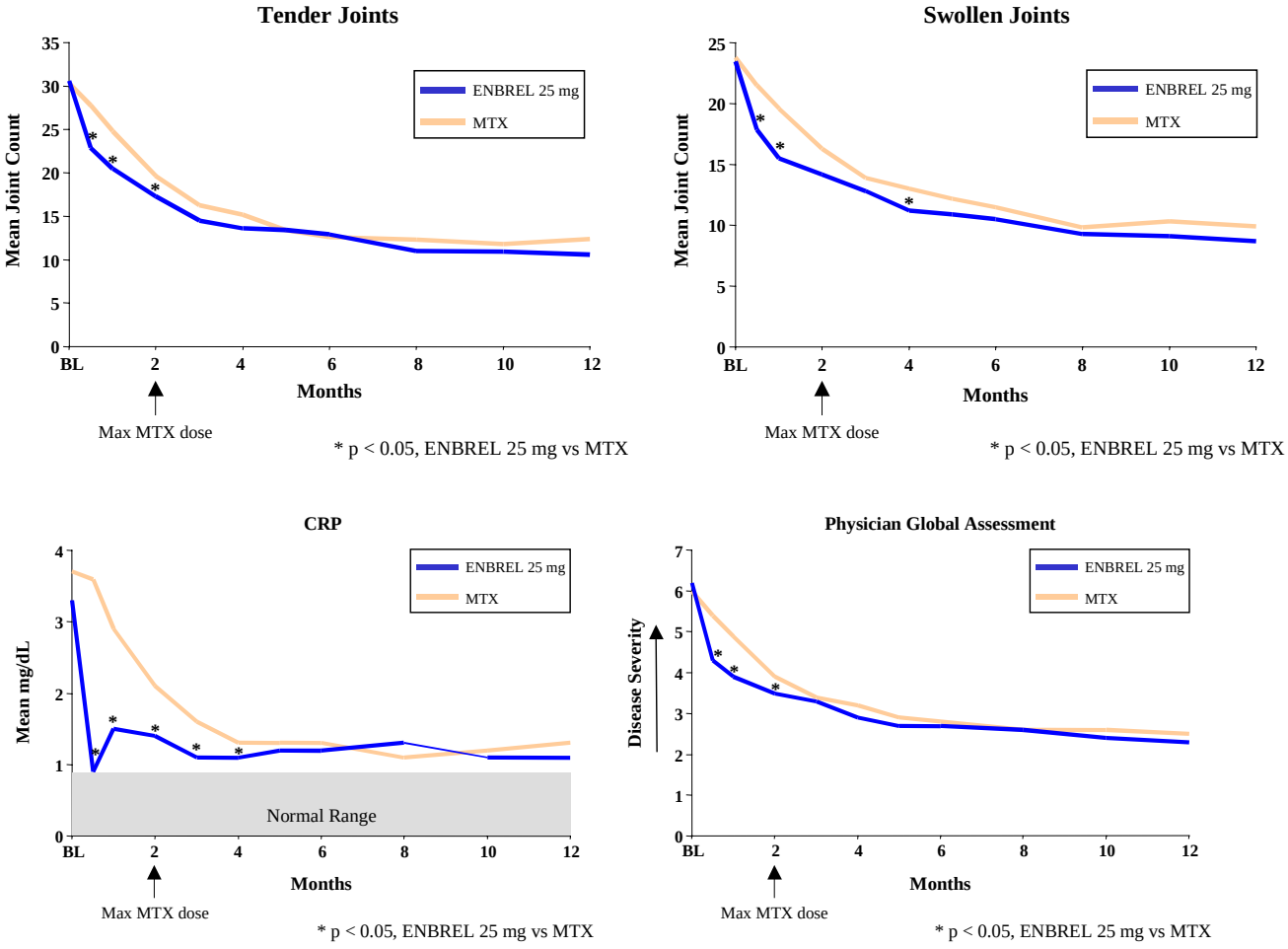


Figure 7.2.3A Individual Arthritis Activity Measures over 12 Months

Patients in all three treatment groups showed substantial improvement in disease activity measures. In general, patients receiving Enbrel 25 mg had greater improvement from baseline than patients receiving MTX within the first 6 months of the trial. A dose response was evident when the 10 and 25 mg Enbrel groups were compared, with Enbrel 25 mg being the most effective.

7.2.4 Other Endpoints

7.2.4.1 Health-Related Quality of Life

Scores at baseline were similar among treatment groups. The mental component summary (MCS) was slightly below US norms and improved to slightly above US norms by 12 months in all 3 groups. As expected for the physical component summary (PCS), the mean score at baseline was well below US population norms. The PCS improved at 12 months in all 3 treatment groups, with 25 mg significantly more effective than 10 mg (p = 0.002), as shown below.

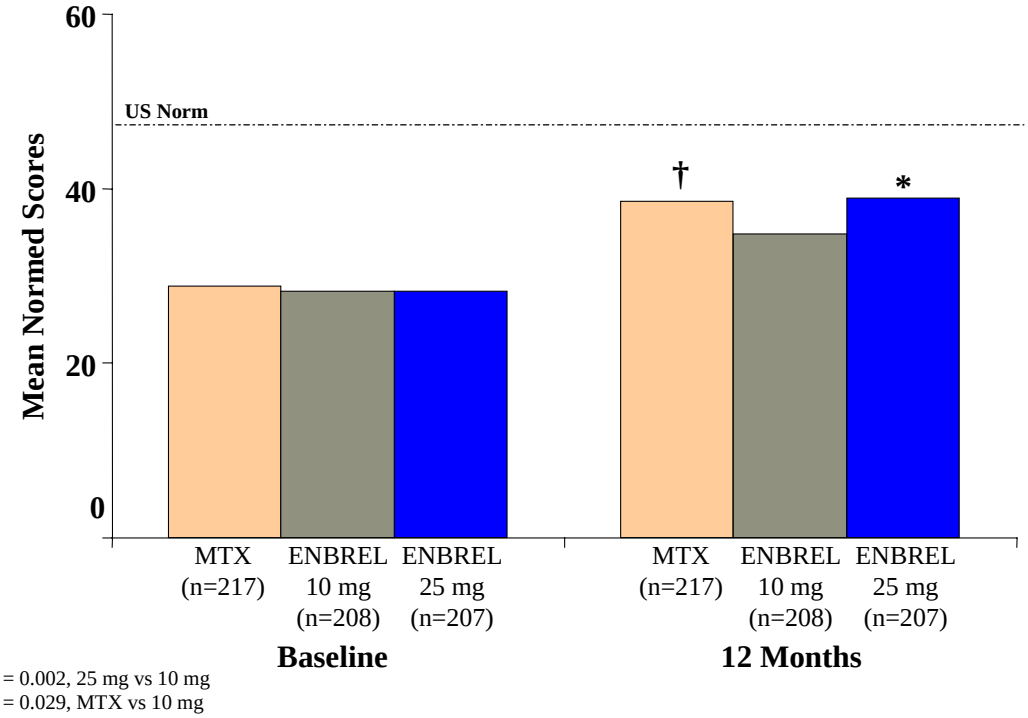


Figure 7.2.4.1A Physical Component Summary Scores at 12 Months

7.2.4.2 Prevention of Disability

The mean baseline HAQ disability scores were in the range of 1.4-1.5 (on a scale of 0 to 3); this indicates moderate disability in the study population despite their relatively short duration of disease. Patients in all groups improved with treatment by month 3 and

showed sustained improvement thereafter. The HAQ scores over time for Enbrel 25 mg and MTX are shown in the following figure.

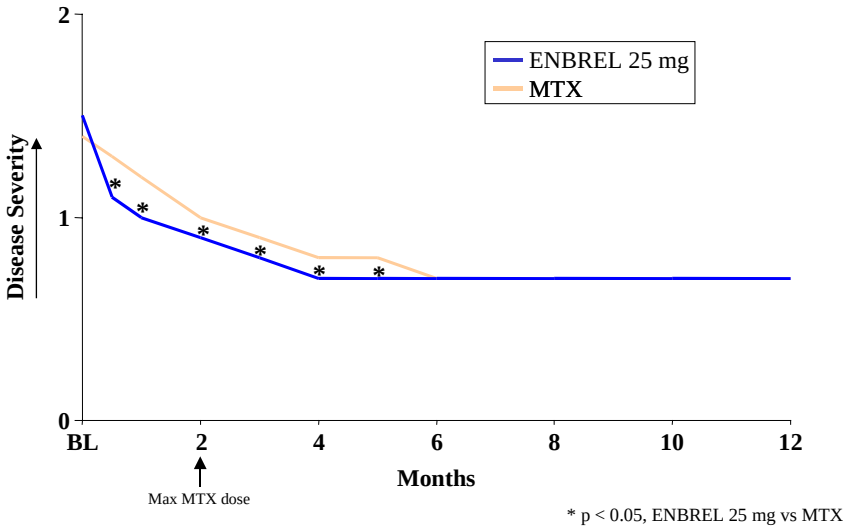


Figure 7.2.4.2A HAQ Disability Index over 12 Months

The percent of patients who had a meaningful change in HAQ score from baseline (at least a 0.5 unit change) was compared among the 3 treatment groups. A 0.5 unit improvement represents a substantial reduction in disability. Results for MTX and Enbrel 25 mg are illustrated in the following figure.

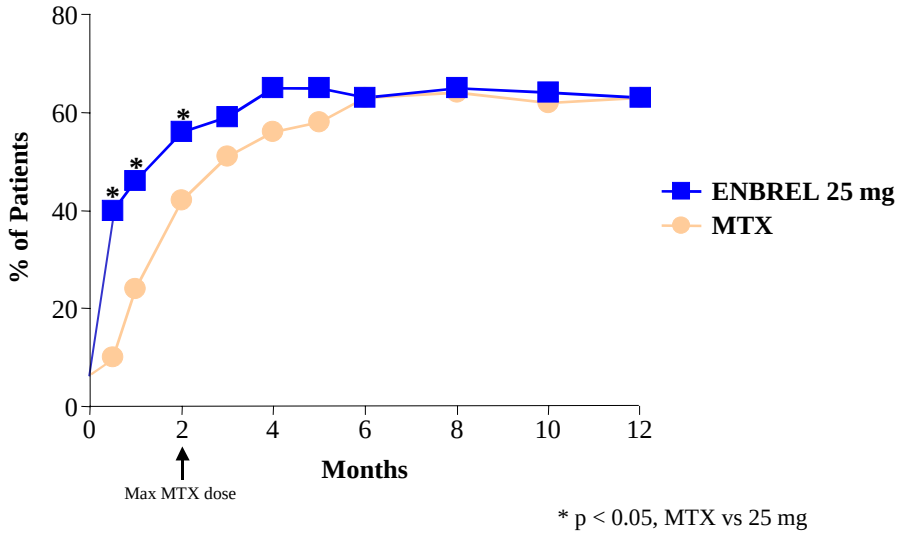


Figure 7.2.4.2B Percent of Patients with at Least 0.5 Unit Improvement in HAQ Score

Patients in both groups showed improvement in HAQ score. The onset of response was more rapid in the Enbrel 25 mg group. By month 12, approximately 60% of all treated patients in both treatment groups had improved by at least 0.5 units.

8.0 Results of Safety Analysis

8.1 Extent of Exposure

The extent of exposure to Enbrel and MTX while patients were on study drug is summarized in the table below.

Table 8.1A Extent of Exposure at 12 Months

	SC Study Drug			Oral Study Drug		
	Placebo	Enbrel		MTX	Placebo	
Parameter	N = 217	10 mg N = 208	25 mg N = 207	N = 217	10 mg N = 208	25 mg N = 207
Mean number of doses	93	93	95	46	46	48
Mean cumulative dose (mg per pt.)	N/A	930	2375	805	N/A	N/A

During the 12-month trial, the number of doses of SC study drug were comparable across treatment groups, as were the number of oral doses of study drug.

8.2 Deaths

There were 2 deaths during the 12-month study period. One patient in the Enbrel 10 mg group died of metastatic lung cancer and 1 patient in the Enbrel 25 mg group died of perioperative complications following emergency repair of a pre-existing aortic aneurysm. Both deaths were considered by the investigators to be unrelated to Enbrel.

8.3 Serious Adverse Events (SAEs)

An adverse event is defined as serious if it results in death, is life-threatening, results in persistent or significant disability, results in drug dependency or abuse, requires inpatient hospitalization or prolonged hospitalization, is a congenital anomaly, or is a symptomatic overdose. An SAE also includes any important medical event that jeopardizes the patient or requires medical or surgical intervention to prevent one of the outcomes listed (21 CFR 312.32). The SAEs that occurred in this study are summarized in the following table.

Table 8.3A Patients with SAEs*

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Infection	5	2	4
Malignancy	2	2	3
Interstitial pneumonitis	3	0	0
Myocardial infarction/angina	3	3	0
Pulmonary embolism/deep vein thrombosis	0	2	2
Other	9	3	8
Total no. patients (%)	18 (8.3)	9 (4.3)	15 (7.2)
Total no. events	22	14	18

* Some patients had more than one SAE.

The frequency and rate of SAEs that occurred in this study were similar in all 3 treatment groups. MTX-induced interstitial pneumonitis occurred in 3 patients in the MTX group and no patients treated with Enbrel. Treatment group was unblinded for the 3 patients in the MTX group; other etiologies (infection, pulmonary emboli, etc.) for the interstitial pneumonitis were excluded. The 3 patients were hospitalized for 8 to 9 days each.

8.4 Infections Requiring Hospitalization or IV Antibiotics

Infections that required hospitalization or IV antibiotics occurred infrequently and were seen in 6 patients in the MTX group, 2 in the Enbrel 10 mg group, and 4 in the Enbrel 25 mg group. This is summarized in the following table.

Table 8.4A Patients with Infections Requiring Hospitalization or IV Antibiotics*

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Bacteremia	1**	1 †	0
Cystitis	1	0	0
Pneumonia	3	1	3
Pyelonephritis	1	0	0
Sepsis	0	0	1 ‡
Septic arthritis	0	1	0
Total no. patients (%)	6 (2.8)	2 (1.0)	4 (1.9)
Total no. infections	6	4	5

* Some patients had more than one event.
** Associated with diverticulitis
† Associated with supraclavicular cyst
‡ Associated with pneumonia

Serious infections were uncommon. As expected, pneumonia was the most common serious infection, seen in 3 patients in the MTX group, 1 in the Enbrel 10 mg group, and 3 in the Enbrel 25 mg group. Study drug was permanently discontinued due to a serious infection for 2 patients in the MTX group, 2 patients in the Enbrel 10 mg group, and 1 patient in the Enbrel 25 mg group. No opportunistic infections or deaths associated with infection occurred.

8.5 Malignancy

Excluding non-melanoma skin cancer, there were 7 cases of malignancy in this trial. There were 2 cases in the MTX group (colon and bladder), 2 cases in the Enbrel 10 mg group (breast and lung), and 3 cases in the Enbrel 25 mg group (carcinoid tumor of the lung, Hodgkin's disease, and prostate). The observed rates of cancer in each group were compared to the expected rates calculated using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database (Kosary 1995) for an age and sex matched general US population. Observed rates were similar to the expected rates of 1.8 in the MTX group, 1.9 in the Enbrel 10 mg group, and 2.0 in the Enbrel 25 mg group.

There was no evidence of increased rates of cancer when compared to expected rates in the general population.

8.6 Discontinuations for Safety Reasons

There were more discontinuations due to adverse events in the MTX group than in both Enbrel groups combined; 10% of patients in the MTX group compared to 4% in the Enbrel 10 mg group, and 5% in the Enbrel 25 mg group (p = 0.016, MTX vs all Enbrel).

Table 8.6A Patients Who Discontinued Study Drug due to Adverse Events

	MTX	Enbrel	
Adverse Event	**N = 217**	**10 mg N = 208**	**25 mg N = 207**
Infection	3	3	1
Malignancy	1	2	2
Interstitial pneumonitis	3	0	0
Rash/mouth ulcer/alopecia/epistaxis	7	1	1
Injection site reactions	0	0	1
Other	7	3	5
Total no. patients (%)	21 (10)*	9 (4)	10 (5)

* p = 0.016, MTX vs all Enbrel.

8.7 Adverse Events

All treatment-emergent adverse events (those that started or worsened on or after the date of the first dose of study drug) were summarized regardless of their relationship to study drug treatment, other concomitant treatment, or the underlying disease process. More MTX-treated patients (95%) had adverse events compared to patients receiving Enbrel, and this difference reached statistical significance for both the Enbrel 10 mg group (90%, p = 0.039) and the Enbrel 25 mg group (89%, p = 0.017). The following table summarizes adverse events that were either significantly more common in MTX-treated patients or significantly more common in Enbrel-treated patients.

Table 8.7A Adverse Events Associated* with MTX or Enbrel Occurring in > 5% of Patients

	MTX	Enbrel	
		10 mg	25 mg
Adverse Event	**N = 217**	**N = 208**	**N = 207**
Injection site reaction	7%	30% *	37% *
Nausea	29% *	14%	17%
Rash	23% *	16%	12%
Mouth ulcers	14% *	6%	5%
Epistaxis	7% *	1%	2%

* $p < 0.05$ overall and $p < 0.05$ MTX vs all Enbrel

Some toxicities, including nausea, rash, mouth ulcers, and epistaxis, are commonly seen with MTX use. As expected, these toxicities occurred significantly more frequently in the MTX group in this study.

As seen in other Enbrel studies, injection site reactions (ISRs) were associated with Enbrel treatment. Significantly more Enbrel patients developed ISRs compared to the MTX patients. In the MTX group, 7% of patients had an ISR from placebo injection, compared with 30% in the Enbrel 10 mg group ($p < 0.001$) and 37% in the Enbrel 25 mg group ($p < 0.001$). Of the patients who received Enbrel, the majority (66%) did not have an ISR. The frequency of ISRs in the Enbrel groups was similar to that seen previously in controlled trials of Enbrel 25 mg in DMARD-refractory RA patients (37%; Enbrel® package insert).

All ISRs were of Grade 1 or 2 intensity. Grade 1 intensity was defined as redness only, and Grade 2 was defined as pain and/or swelling and/or pruritus, with or without redness. No treatment was given for the majority (86%) of ISRs in the Enbrel treatment groups. Of the patients in the Enbrel groups who did have ISRs, the majority (69%) had 5 or fewer reactions over a maximum of 104 injections a patient could receive in the first year of drug administration. One patient in the Enbrel 25 mg group discontinued study drug due to a Grade 2 ISR. No other patients had study drug interrupted or withdrew from study due to ISRs.

ISRs tended to occur early in the study in patients on Enbrel (first occurrence at a median of 15 days) and decreased over time. This time course was similar to that observed in patients with long-standing RA in earlier trials.

8.8 Overall Incidence of Infections

Infections were reported in 72% of the patients in the MTX group, 61% in the Enbrel 10 mg group, and 67% in the Enbrel 25 mg group. The overall incidence, type, and rate of infections per patient-year are shown in the following table.

Table 8.8A Overall Incidence of Infection

	MTX	Enbrel	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Infections by type	**(193 pt-yr)**	**(185 pt-yr)**	**(189 pt-yr)**
Any type:			
Patients with infections	72%	61%*	67%
No. infections per patient-year	1.91	1.54**	1.54**
URI:			
Patients with infections	39%	27%*	35%
No. infections per patient-year	0.61	0.45	0.54
Non-URI:			
Patients with infections	60%	51%	51%
No. infections per patient-year	1.30	1.08	0.99**

All p values are comparing MTX group to each Enbrel group
* $p < 0.05$, Fisher's exact test
** $p < 0.01$, exact binomial test

Patients in the MTX group had a higher rate of infections than patients in the Enbrel groups. The infections reported were generally typical of infections seen in an outpatient adult population.

8.9 Laboratory Evaluations

The majority of abnormal laboratory results were of mild to moderate (Grade 1 or 2) intensity. All laboratory abnormalities that occurred at any time on study were

summarized. Those occurring at a higher frequency in the MTX or Enbrel groups are presented in the following table.

Table 8.9A Laboratory Abnormalities with Higher Frequency in MTX or Enbrel Groups

	MTX	Enbrel	
		10 mg	25 mg
Laboratory Parameter	N = 217	N = 208	N = 207
Chemistry			
AST (high)[a]	32% *	15%	16%
ALT (high)[a]	44% *	23%	24%
Hematology			
ANC (low)[b]	8%	10%	16% **
Lymphocytes (low)[c]	79% *	68%	56%

a greater than the upper limit of normal
b ANC <2000 cells/cmm
c lymphocytes <1500 cells/cmm
* $p < 0.001$, MTX vs combined Enbrel
** $p = 0.012$, MTX vs Enbrel 25 mg

Elevated liver function tests (ALT, AST) and low lymphocyte counts occurred at significantly higher frequencies in the MTX group. Approximately twice as many patients taking MTX as patients taking Enbrel had elevations of AST (32% vs 16%, MTX vs all Enbrel; $p < 0.001$) or ALT (44% vs 23%, MTX vs all Enbrel; $p < 0.001$). Similarly, patients taking MTX were more likely to have a low lymphocyte count than those taking Enbrel (79% vs 62%, MTX vs all Enbrel; $p < 0.001$). Patients taking Enbrel 25 mg experienced transient neutropenia without clinical sequelae more frequently than patients taking MTX (16% vs 8%, MTX vs Enbrel 25; $p = 0.012$). No patient discontinued study drug due to neutropenia. The majority (73%) of low neutrophil counts in all groups were grade 1 (ANC < 2000 but ≥ 1500 cells/cmm).

Treatment-emergent, grade 3 abnormal laboratory results that occurred during the 12-month study period are listed in the following table. There were no Grade 4 abnormal laboratory results.

Table 8.9B Number of Patients with Any Grade 3 Abnormal Laboratory Results During the Study*

Parameter	Grade	Grade 3 Range	MTX N = 217	Enbrel 10 mg N = 208	Enbrel 25 mg N = 207
Any abnormality	3	N/A	18	8	3
Chemistry					
Albumin (low)	3	≥ 2.0 - < 2.6 g/dL	0	1	0
AST (high)	3	> 5.0 x N - ≤ 20.0 x N IU/L	1	1	0
ALT (high)	3	> 5.0 x N - ≤ 20.0 x N IU/L	4	2	0
Hematology					
ANC (low)	3	≥ 0.5 - < 1.0 x 1000 cells/cmm	2	1	3
Hemoglobin (low)	3	≥ 6.5 - < 8.0 g/dL	1	0	0
Lymphocytes (low)	3	< 0.5 x 1000 cells/cmm	12	4	0
WBC (low)	3	≥ 1.0 - < 2.0 x 1000 cells/cmm	1	0	0

*Some patients had more than one abnormal test result

Grade 3 abnormal laboratory results were infrequent in all 3 treatment groups during the first year in this study.

8.10 Antibody to Enbrel

Serum samples to be analyzed for antibody to Enbrel were to be collected before administration of study drug on Day 1, at the end of weeks 26 and 52, and at study completion or premature discontinuation from the study. Samples from 24 patients were not tested because either prestudy or on-study samples were not available. This included 10 patients in the MTX group, 10 patients in the Enbrel 10 mg group, and 5 patients in the Enbrel 25 mg group. Test results are shown in the following table.

Table 8.10A Anti-Enbrel Antibody Formation:

No. of Patients Testing Positive at Any Time

	MTX	Enbrel	
		10 mg	25 mg
	N = 207	N = 198	N = 202
Assay	n (%)	n (%)	n (%)
ELISA	0	5 (2.5)	6 (3.0)
Neutralizing	0	0	0

No patients who received MTX tested positive in the ELISA. Of the patients who received Enbrel, 11 (2.8%) had at least 1 positive test in the ELISA (5 patients in the Enbrel 10 mg group and 6 patients in the Enbrel 25 mg group). None of the 11 patients had a positive test for neutralizing antibody. Seven of the 11 patients had subsequent negative tests for anti-Enbrel antibodies and 8 of the 11 patients remain on Enbrel. There was no relationship between safety or efficacy and the presence of these antibodies.

8.11 Long-term Safety in Other Trials

Long-term safety of Enbrel in other RA trials is summarized in Appendix A.

9.0 Summary

9.1 Summary of Efficacy

The primary efficacy endpoints are summarized in the following table.

Table 9.1A Summary of Primary Efficacy Endpoints

	MTX	Enbrel		Enbrel 25 mg vs MTX	
		10 mg	25 mg	p value	Goal
STRUCTURAL DAMAGE					
Equivalence Endpoint (progression rate in TSS over 12 months)	1.3	1.4	0.8	NA*	Achieved
Superiority Endpoint (progression rate in erosion score over 12 months)	1.03	0.90	0.47	0.002	Achieved
SIGNS AND SYMPTOMS					
ACR-N AUC over 6 months	11.5	13.0	15.3	0.002	Achieved

*upper limit of one-sided 95% CI = 0.16 which is less than prespecified equivalence limit of 1.2

Results of the ERA study demonstrate that Enbrel is effective in preventing radiographic progression and reducing signs and symptoms in patients with RA.

Enbrel Prevents Structural Damage in RA

The primary equivalence analysis shows Enbrel 25 mg to be at least equivalent to MTX in preventing progression of disease measured radiographically. In order to demonstrate an effect on prevention of structural damage, Enbrel 25 mg was required to preserve at least 70% of the expected benefit of MTX.

The mean changes in TSS over 12 months were 1.3, 1.4, and 0.8 units for the MTX, Enbrel 10 mg, and Enbrel 25 mg groups, respectively. The upper bound of the 1-sided 95% confidence interval for the difference between Enbrel 25 mg and MTX was 0.16 total Sharp units/year, well within the prospectively defined threshold of 1.2 total Sharp units/year. Enbrel 25 mg is estimated to have 113% of the predicted MTX treatment effect and with one-sided 95% confidence it preserves at least 96% of the predicted MTX treatment effect. Another perspective indicating the robustness of the results is that the

equivalence criterion would have been met even if the MTX to placebo effect used was only 0.23 Sharp units. Thus, the primary equivalence endpoint was not only achieved, but was exceeded by a comfortable margin.

Analysis of the superiority endpoint demonstrated that Enbrel 25 mg was significantly more effective than MTX in preventing erosions. The mean change from baseline in erosion score at month 12 for MTX patients was 1.03 units, compared to 0.90 units in Enbrel 10 mg patients, and 0.47 units in Enbrel 25 mg patients (overall $p = 0.005$, pairwise Enbrel 25 mg vs MTX $p = 0.002$). In the Enbrel 25 mg group, 72% had no progression in erosion score at 12 months, compared to 60% in the MTX group ($p = 0.007$). The three treatment groups showed similar low rates of progression of JSN.

MTX, rapidly escalated and given at 20 mg/week, also performed well in this study, particularly when compared with the literature. This is even more noteworthy if one takes into account the highly active characteristics of the RA in this patient population.

Enbrel Reduces Signs and Symptoms of RA

Enbrel 25 mg was effective in reducing signs and symptoms of RA in patients in this study. The mean ACR-N AUC over 6 months was 11.5, 13, and 15.3 units (ACR-N•year) for the MTX, Enbrel 10 mg, and Enbrel 25 mg groups, respectively (overall $p = 0.006$, pairwise Enbrel 25 mg vs MTX $p = 0.002$).

The dose of MTX was escalated in this study from 7.5 to 20 mg per week by week 8. This dose escalation is more rapid than has been utilized in most previous clinical trials and was carried out in this way to ensure that the maximum efficacy of MTX therapy would be observed. Despite the rapid dose escalation of MTX, both Enbrel groups had a more rapid clinical response.

The other clinical endpoints in this study corroborate the primary clinical endpoint and confirm the efficacy of Enbrel in the treatment of signs and symptoms of RA. For all of the individual disease activity parameters, improvement was rapid and sustained.

Clinical improvement correlated with lack of radiographic progression.

9.2 Summary of Safety

As in previous controlled trials of patients with long standing RA and in the long-term open-label safety study (Appendix A), the ERA study demonstrates that Enbrel is generally safe and well tolerated and provides a good benefit-to-risk profile. The safety profile of Enbrel in this study, in patients with active RA treated within 3 years of diagnosis who had not previously been treated with MTX, was similar to that described in previous studies of patients with long-standing, active RA who had not adequately responded to or had failed DMARDs.

Adverse Events

The rate and frequency of adverse events seen in this trial were lower in both groups of patients receiving Enbrel than in patients receiving MTX. These adverse events included both common and serious toxicities attributable to MTX, including nausea, rash, mouth ulcers, epistaxis, and potentially fatal pneumonitis. The latter was observed in 3 patients (1.4%) receiving MTX (who were hospitalized for 8-9 days each) but in none of the patients receiving Enbrel.

As in previous trials, injection site reaction (ISR) was the most common adverse event reported in patients receiving Enbrel (34%). The ISRs that were observed were all Grade 1 or Grade 2 in intensity, typically lasted 3 days, and resolved without therapy. Only 1 patient withdrew from the study because of an ISR.

Deaths

There were 2 deaths in this study, 1 of metastatic lung cancer in the Enbrel 10 mg group and 1 of perioperative complications following emergency repair of a pre-existing aortic aneurysm in the Enbrel 25 mg group. Both deaths were considered by the Investigators to be unrelated to Enbrel.

Infection

The overall rate of all types of infection was higher in patients receiving MTX than in those receiving Enbrel (1.91 events per patient-year in the MTX group versus 1.54 in each Enbrel group, $p = 0.006$). Infections that required hospitalization or intravenous antibiotics were infrequent and occurred in 6 patients in the MTX group, 2 in the Enbrel 10 mg group, and 4 in the Enbrel 25 mg group. Two patients in the MTX group discontinued study drug due to serious infections, compared to 2 patients in the Enbrel 10 mg group and 1 patient in the Enbrel 25 mg group. There were no opportunistic infections and no deaths associated with infections.

Malignancy

There was no evidence of an increased rate of malignancy in any treatment group when compared to national rates in the general population (National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER]). There were 2 cases in the MTX group (colon and bladder), 2 cases in the Enbrel 10 mg group (breast and lung), and 3 cases in the Enbrel 25 mg group (carcinoid lung, Hodgkin's disease, and prostate).

Laboratory Results

There were no unexpected abnormalities in laboratory results in any of the treatment groups. When abnormal laboratory tests that occurred at any time in the study were summarized, elevated liver enzymes (ALT and AST) and low lymphocyte counts occurred at higher frequencies in the MTX group, as would be expected. Transient neutropenia (primarily absolute neutrophil counts $\leq$2000 but greater than 1500 cells/cmm), without clinical sequelae, was seen in 16% of patients in the Enbrel 25 mg group, compared to 8% in the MTX group and 10% in the 10 mg group. The low frequency of abnormal laboratory results in the Enbrel groups is consistent with earlier trials.

Antibody to Enbrel

Three percent of patients in the Enbrel treatment groups developed antibodies to Enbrel. None of the antibodies had neutralizing activity, and there was no relationship between safety or efficacy and the presence or absence of these antibodies.

10.0 Benefit and Risk Assessment

This well-controlled study in 632 patients with early RA demonstrates that Enbrel can prevent structural damage and effectively treat the signs and symptoms of RA.

Enbrel slowed disease progression as measured radiographically. Compared to MTX, which is the most widely used DMARD, Enbrel was at least equivalent in preventing structural damage as assessed by TSS (0.8 units/year for Enbrel 25 mg vs 1.3 units/year for MTX). Furthermore, Enbrel 25 mg was significantly better than MTX in preventing erosions ($p = 0.002$). More patients receiving Enbrel 25 mg had no disease progression as measured by TSS (62% for Enbrel 25 mg vs 56% for MTX) and erosion score (72% for Enbrel 25 mg vs 60% for MTX, $p = 0.007$).

Enbrel produced a statistically significant improvement in response as measured by area under the curve of the numeric ACR Response (ACR-N AUC) over 6 months when compared to optimal oral MTX therapy ($p = 0.002$). Rapid and sustained improvement was observed in each of the individual ACR response criteria. Patients in the Enbrel 25 mg group exhibited marked improvement in health-related quality of life as shown by significant improvement in the SF-36 PCS and normalization of the MCS at 12 months. Enbrel was capable of inducing a major clinical response, as evidenced by 11% of patients in the Enbrel 25 mg group who had a major clinical response.

MTX is an effective treatment, particularly when aggressively dosed to 20 mg/week as in this study. Fifteen percent of those receiving MTX required oral dose reductions due to adverse events (nausea, oral ulcers, alopecia, rash) or abnormal laboratory indices. Of the patients receiving MTX, 10% discontinued oral study drug prior to 1 year due to adverse events, compared to only 5% of the combined Enbrel groups ($p = 0.016$).

Enbrel is generally safe and well tolerated. Injection site reactions (ISRs) were the most common adverse events associated with Enbrel administration. These reactions are of no apparent clinical consequence and decrease in frequency with time on therapy. Significant infections were uncommon and similar in the MTX and Enbrel arms. Overall

infection rates were lower in Enbrel patients (1.91 per patient-year in patients receiving MTX, 1.54 per patient-year in patients receiving Enbrel 25 mg [p = 0.006]).

The safety profile of Enbrel in patients with early active RA is similar to that in patients with long-standing RA. It is estimated that Enbrel has been prescribed to over 65,000 patients since its market introduction in 1998. Immunex continues to monitor spontaneous event reports arising from this marketing experience. The most commonly reported event has been injection site reaction, a finding that is consistent with clinical trial results. The event that has been of major interest is serious infection. To date, infections representing a broad range of organisms have been reported, but the reporting rate has been consistent with the incidence seen in clinical studies. Immunex is currently conducting a post-approval study to address this issue.

Compared to available DMARD therapies and other therapies for RA, Enbrel presents a good benefit-to-risk profile and provides an important option to physicians treating patients with active disease.

11.0 Conclusions

The results of this active controlled trial, which directly compared Enbrel to MTX, demonstrate that Enbrel prevents structural damage and improves signs and symptoms of RA in patients with RA.

Enbrel at the dose of 25 mg twice weekly met prospectively defined criteria to demonstrate both equivalence to MTX for preventing structural damage using the TSS and superiority to MTX in preventing erosions using the erosion score alone. These findings support the conclusion that Enbrel is an important treatment option that will prevent structural damage in patients with RA and justifies the classification of Enbrel as a "DMARD."

Furthermore, consistent with previous studies of RA patients with long-standing disease, Enbrel also provides significant benefit in the reduction of signs and symptoms of patients with early RA. Compared to patients treated with MTX, patients treated with Enbrel 25 mg had a faster onset of clinical response and that response was sustained over the 12-month study period.

Enbrel is well tolerated and has a good benefit-to-risk profile.

Enbrel at 25 mg provides rapid, substantial, durable, and comprehensive improvement to patients with RA and is a valuable addition to treatment options available to patients and physicians to use in early as well as in long standing RA.

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Appendix A

Long-Term Experience with Enbrel

1.0 Introduction

Because RA is a chronic disease that requires life-long therapy, the cumulative safety profiles of RA therapies are a central concern. This document primarily summarizes the long-term safety profile of Enbrel seen in North America.

The most extensive safety database regarding long-term therapy with Enbrel is the North American experience that includes a total of 782 patients from 9 previous Enbrel trials. They have received continued treatment in an ongoing long-term safety study and total 1352 patient-years of Enbrel therapy. The longest duration of Enbrel therapy is 43 months.

Additional safety data had been obtained from the Wyeth-Ayerst European Enbrel program. In Europe, patients enrolled in 2 placebo-controlled trials were allowed further Enbrel therapy in a long-term open-label trial. In this program, 612 patients have been treated for a total of 554 patient-years. Although not included in this summary, the long-term safety profile in European trials is consistent with the North American experience.

Table 1.0A Patients in Global Clinical RA Trials

Exposure	Total Number of Patients	Total Patient-Years
North American Trials	782	1352
European Trials	612	554
Total	1394	1906
ERA + ERA Continuation	447	694
Grand Total	1841	2600

Table 1.0B Enbrel Exposure in Global Clinical RA Trials*

Length of Treatment	Total Number of Patients	ICH Guidelines
Any	1841*	1500
≥ 6 months	1531	300-600
≥ 12 months	1425	100
≥ 24 months	436	
≥ 36 months	53	

* an additional 700 patients have received Enbrel in trials in other diseases

2.0 Adverse Events in North American Long-Term Study

Longer term exposure to Enbrel has not been associated with an increase in adverse events compared with short-term therapy used in the controlled clinical trials. Eighty-eight percent of patients in this database have been treated at the recommended dose of 25 mg Enbrel administered subcutaneously (SC) twice weekly. Seventy-seven percent of patients were female. The mean age was 51 years. Most patients had long-standing RA, with a mean duration of 12 years. The mean number of previous DMARDs was 3.

Adverse events reported in long-term experience are not greater than in controlled clinical trials and are similar to placebo, as shown in the following table.

Table 2.0A Adverse Events Rates in North American Studies*

	Controlled Trials		Long-Term
	Placebo N = 152	Enbrel N = 349	Enbrel N = 782
Headache	0.62	0.68	0.33
Rash	0.12	0.21	0.17
Nausea	0.47	0.30	0.16
Rhinitis	0.35	0.45	0.16
Diarrhea	0.35	0.27	0.12

* rates are per patient-year

3.0 Infections

3.1 Infections in North American Clinical Database

In controlled trials, there was no increase in the frequency or severity of infections in Enbrel-treated patients than in placebo-treated patients. Furthermore, longer exposure did not lead to an increase in the rate of infections. Most infections were considered mild or moderate. Occasionally, a more serious infection occurred. To objectively review these infections and to observe rates of infections over time, infections requiring hospitalization or non-prophylactic intravenous antibiotics were identified. These potentially serious infections also have not increased with more prolonged exposure to Enbrel.

Table 3.1A Infection Rates in North American Study

	Controlled Trials		Long-Term
	Placebo N = 152	Enbrel N = 349	Enbrel N = 782
All infections	1.86	1.82	1.67
Infections requiring hospitalization or IV antibiotics	0.050	0.043	0.048

* rates are per patient-year

Most of the infections reported in this study were consistent with those commonly seen in outpatient adult populations (Andriole 1988; Dingle 1973; Dolin 1998; Gwaltney 1995). Infections requiring hospitalization or IV antibiotics occurred at similar rates in the placebo and Enbrel groups in the controlled trials and in the long-term trial. Of the patients who experienced these more serious infections, 72% continue to receive Enbrel.

The available medical literature indicates that serious infections occur frequently in patients with RA (Ramey 1999), and that mortality due to infectious causes is higher in patients with RA than in the general population (Duthie 1964; Wolfe 1994) and ranges from 0.39 to 1.28 per 100 patient-years. This is summarized in the following table.

Table 3.1B Infection-associated Mortality in Rheumatoid Arthritis

Source	Year of Publication	Number of Patients	Estimated exposure (patient-years)	Estimated mortality/ 100 patient-years
Duthie et al. (UK)	1964	307	2,240	0.49
Prior et al. (UK)	1984	489	5,018	0.64
Schnabel et al.* (Germany)	1996	168	313	1.28
Van den Borne et al. (Netherlands)	1998	415	2,280	0.39

* patients receiving methotrexate more than 15 mg/week

The rate of infection-related mortality in this database is 0.15 per 100 patient-years and compares favorably to the literature.

4.0 Malignancy

Patients in the Enbrel safety database were compared to the general population using the NCI's SEER database (Kosary 1995). There were ten reported cases of cancer, the same as the expected number (11.6) that was calculated by multiplying the SEER age/sex-specific rate times patient-years (in calendar time) in the age/sex category and summing over age/sex categories. Therefore, the rate of cancer occurrence in the long-term study was no higher than expected in the general population. In addition, no predominant cancer type was seen in the study, but rather a representative sampling of the most common cancers occurring in the general population.

5.0 Deaths

In 1352 patient-years of follow-up, 11 patients have died, a rate of 0.8 deaths per 100 patient-year of follow-up. Causes of death have included cardiac (5), cancer (2), infection (or presumed infection) (2), accidental (1), post-operative bleed (1).

6.0 Efficacy in Long-Term Study

Efficacy of Enbrel in patients with RA has continued as long as patients have continued therapy. Adult patients on Enbrel have been followed as long as 43 months. Disease activity measures improve rapidly after initiation of Enbrel monotherapy, and this improvement is sustained over time, as demonstrated in the following figures.

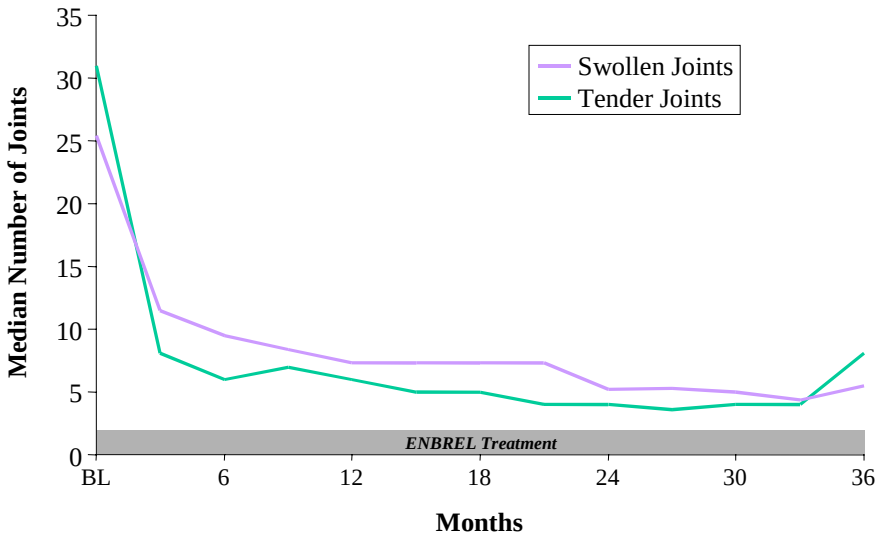


Figure 6.0A Swollen and Tender Joint Scores

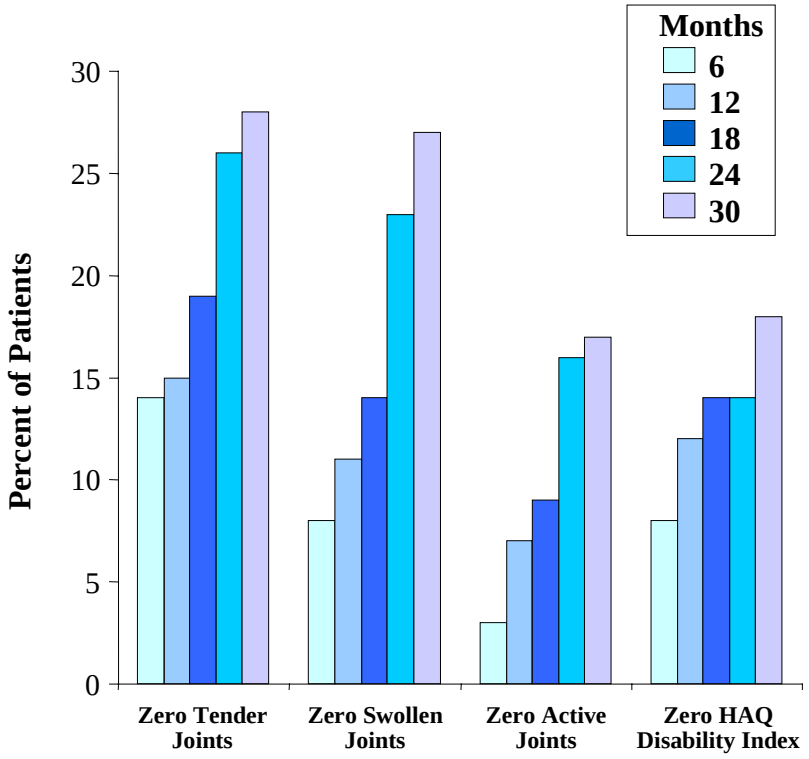
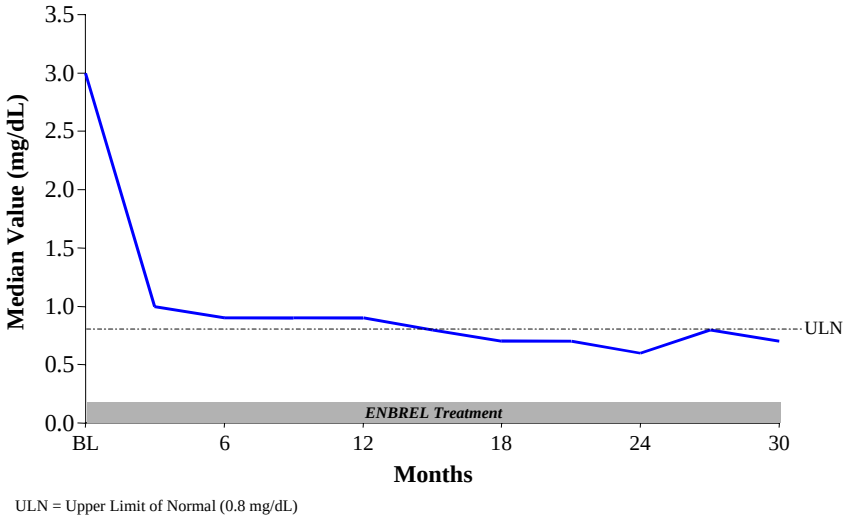


Figure 6.0B 100% Improvement of Individual Disease Parameters



ULN = Upper Limit of Normal (0.8 mg/dL)

Figure 6.0C C-Reactive Protein Levels

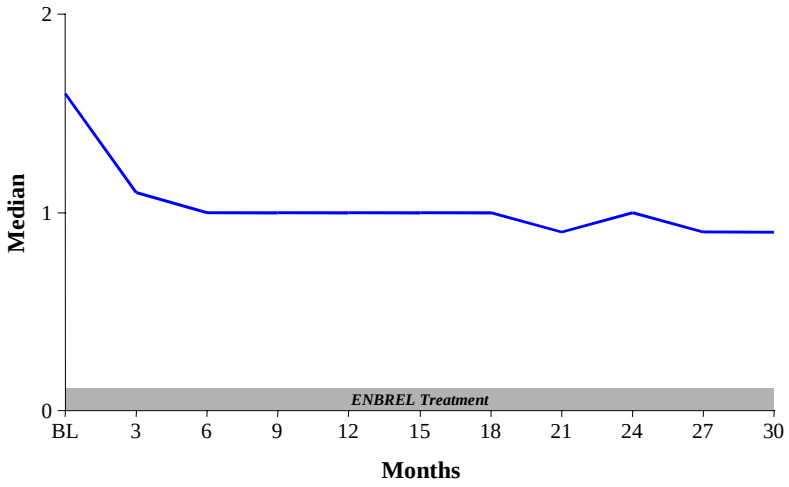


Figure 6.0D HAQ Disability Index

7.0 Conclusion

The safety profile of longer-term administration (up to 43 months) of Enbrel remains consistent with the data previously described in clinical trials. Rates and types of adverse events, including infections, have remained similar to those seen in controlled clinical trials. Cancer occurrence is not higher than would be expected in an age- and sex-matched group from the general population. Enbrel continues to have a good benefit-risk profile, and the efficacy of Enbrel is sustained with continued therapy.

Appendix B

Statistical Appendix

1.0 Radiographic Equivalence Endpoint

The primary radiographic endpoint was to compare the progression of joint damage among the three treatment groups over 12 months using total Sharp score (TSS). As described in Section 3.4.1, equivalence would be demonstrated if Enbrel 25 mg preserved 70% of the expected benefit of MTX. Based on current literature, the rate of progression of TSS in untreated patients was predicted to be approximately 6 units/year and the rate of progression in the MTX group was predicted to be approximately 2 units/year. Thus the expected MTX benefit is 4 TSS units/year. In order to preserve 70% of the expected benefit, the difference between Enbrel 25 mg and MTX in change in TSS at 12 months would have to be less than 1.2 units (i.e., 30% of the expected MTX benefit of 4 units/year).

1.1 Model and Assumptions

The primary analysis was performed using a random coefficients regression model. This is a type of linear mixed effects model in which the response variable is assumed to change linearly with time, while allowing the intercept and the slope to vary with the subject. As specified in the protocol, the effects for disease duration stratum and reader pair were included in the model. The resulting model for the TSS (Y) for the i^{th} subject at time j (X_{ij}) is given by

$$Y_{ij} = \alpha_i + \beta_i X_{ij} + e_{ij}$$

where the within-subject error terms, e_{ij}, are assumed to be independent and identically distributed with a $N(0, \sigma^2)$ distribution. The intercept takes the form

$$\alpha_i = \mu_o + \mu_i + \lambda_i + \delta_i$$

where μ_o is the population average intercept, μ_i is the fixed effect for subject i's disease duration stratum, λ_i is the fixed effect for subject i's reader pair, and δ_i is the subject-

level intercept disturbance. The slope takes the form

$$\beta_i = \tau_i + \gamma_i + \varepsilon_i$$

where τ_I is the population average slope for subject i's randomized treatment, γ_j is fixed effect for subject i's disease duration stratum, and ε_i is the subject-level slope disturbance. The subject-level intercept and slope disturbances $(\delta_I, \varepsilon_I)$' are independent and identically distributed with a N(**0**, **D**) distribution, independent of the e_{ij}. The covariance matrix **D** was assumed to be unstructured.

The distribution of TSS values is non-normal and highly skewed, as evidenced by the baseline values summarized in the following figure.

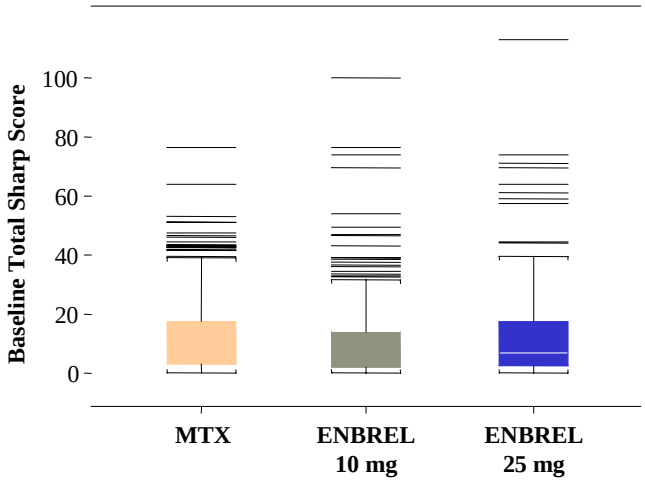


Figure 1.1A Boxplot of Baseline TSS by Treatment Group

A plot of standardized residuals versus the fitted values from the model identifies the presence of outliers.

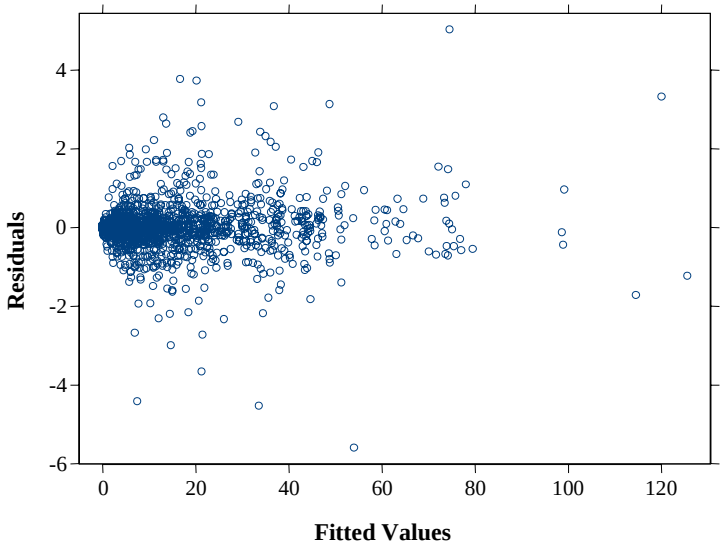


Figure 1.1B Standardized Residuals versus Fitted Values from the Random Coefficients Model Analysis

In this trial in early, active RA, all three treatment groups demonstrated 12-month progression rates much lower than what is predicted for untreated patients, with many patients experiencing no change in TSS over the 12-month course of the trial. This is seen in the low mean 12-month changes in TSS predicted by the model, 1.3, 1.4 and 0.8 units for the MTX, Enbrel 10 mg and Enbrel 25 mg groups, respectively, and is also seen in the normal quantile-quantile plot which indicates the large number of values for which the residual is small (i.e., patients who had no change).

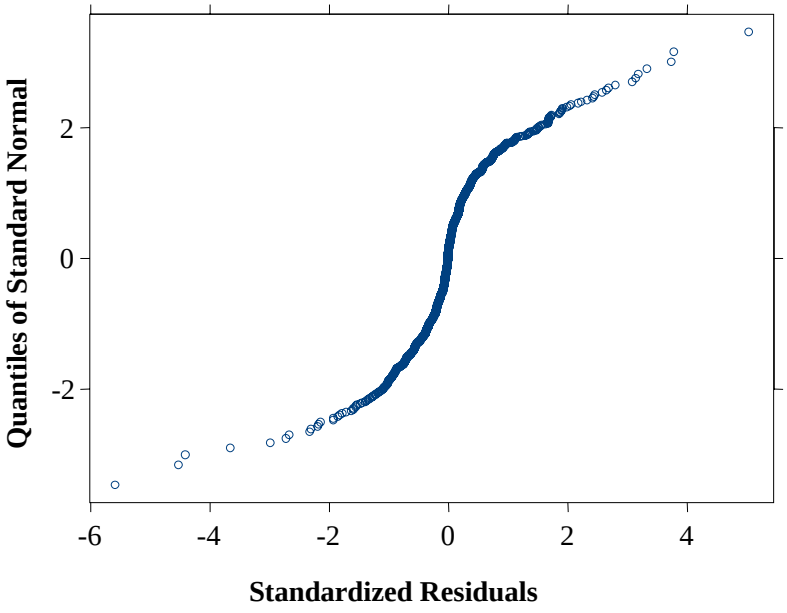


Figure 1.1C Normal Quantile-Quantile Plot for Random Coefficients Model Analysis

The protocol-specified primary analysis of TSS using the random coefficients model showed no statistically significant difference between the Enbrel 25 mg and MTX treatment groups (p=0.212), and the upper endpoint of the one-sided 95% confidence interval for the difference was 0.16. The pre-specified criteria for equivalence was met.

1.2 Non-Parametric Analysis

As an alternative to the random coefficients model analysis, changes from baseline in TSS were examined using a last-observation-carried-forward (LOCF) approach. For patients who had a missing post-baseline x-ray film, the previous value was carried forward, where a linear extrapolation was used to project the result to the time of the missing visit. These changes were compared between treatment groups using the Van Elteren stratified rank test (controlling for disease duration stratum). Results of these analyses for the 6 Month and 12 Month timepoints are summarized in the following table.

Table 1.2A Non-Parametric Analyses of Total Sharp Score

Mean of Actual Change Scores with LOCF

		Enbrel		25 mg vs MTX
Timepoint	MTX	10 mg	25 mg	p-value
6 Month	1.0	0.8	0.6	0.001
12 Month	1.6	1.6	1.0	0.110

The results of the non-parametric analyses at Month 12 are consistent with those obtained from the random coefficients model: The non-parametric analysis estimates a slightly larger difference in 12 month progression rates between MTX and 25 mg (0.6 units/year versus 0.5 units/year from the random coefficients model), and the p-value for the treatment comparison is lower (0.110 versus 0.212 from the random coefficients model).

1.3 Robustness of Equivalence Limit

Based upon the random coefficients model analysis, the point estimate for the difference between MTX and Enbrel 25 mg in TSS progression rates is -0.53 units/year (favoring Enbrel 25 mg); this would suggest Enbrel 25 mg maintains 113% of the predicted benefit of MTX (i.e., 4+0.53/4). The upper endpoint of the 95% one-sided confidence interval for the difference between MTX and Enbrel 25 mg for change in TSS is 0.16. This is substantially below the pre-defined equivalence level of 1.2 units, demonstrating that Enbrel 25 mg maintains at least 70% of the predicted benefit of MTX. Further, if the rate of progression in TSS in untreated patients is predicted to be approximately 6 units/year and the rate of progression in the MTX group is predicted to be approximately 2 units/year, then the data from this trial indicate that Enbrel 25 mg maintains at least 96% of the predicted benefit of MTX (i.e., (4 – 0.16) / 4).

This demonstration of equivalence is robust to deviations in the assumptions of predicted TSS 12-month progression rates, as shown in the following table.

Table 1.3A Percent of Predicted Benefit Maintained by Enbrel 25 mg as a Function of Untreated and MTX Predicted Progression Rates (TSS units/year)

Rate on	Rate on MTX			
Placebo	1	1.5	2	2.5
3	92	89	84	68
4	95	94	92	89
5	96	95	95	94
6	97	96	96	95
7	97	97	97	96
8	98	98	97	97

Even had the predicted MTX benefit been as little as 0.23, equivalence criteria would still be met; 70% of 0.23 is 0.16.

2.0 Original Radiographic Superiority Endpoint

The primary radiographic endpoint specified in the original protocol was to compare progression of joint damage among the three treatment groups over 12 months using Sharp erosion score. The primary analysis of erosion score was an intent-to-treat analysis using a last-observation-carried-forward (LOCF) technique in the presence of missing post-baseline data, where a linear extrapolation was used project the result to the time of the missing visit. Comparisons among treatment groups were made using the Van Elteren stratified rank test (controlling for disease duration stratum). Results of these analyses for the 6 Month and 12 Month timepoints are summarized in the following table.

Table 2.0A Non-Parametric Analyses of Erosion Score

Mean of Actual Change Scores

	Treatment Group			25 mg vs MTX
Timepoint	MTX	10 mg	25 mg	p-value
6 Month	0.68	0.50	0.30	0.001
12 Month	1.03	0.90	0.47	0.002

As a comparison, the random coefficients model analysis of 12 month progression rates in erosion score also identifies a statistically significant difference between the MTX and Enbrel 25 mg treatment groups (p=0.047).

2.1 Missing Data

Compliance with scheduled x-ray evaluations was high; 92% of patients had at least three x-rays. One patient with no x-ray films was excluded from all analyses of radiographic endpoints. The robustness to mechanisms of handling missing data was examined under two alternative schemes. A completers' analysis was performed using only those patients who had an x-ray evaluation performed within two weeks prior to the scheduled visit or anytime thereafter; this was irrespective of compliance with study drug. The other alternative scheme examined was the LOCF approach without the extrapolation of early results. The following table illustrates that regardless of the mechanism employed there is a statistically significant difference between Enbrel 25 mg and MTX on the erosion score endpoint.

Table 2.1A Results of Non-Parametric Statistical Analyses of Change in Erosion Score Comparison of Enbrel 25 mg and MTX

Timepoint	LOCF with extrapolation	LOCF without extrapolation	Completers
6 Month	P=0.001 (n=631)	P=0.001 (n=631)	P=0.001 (n=609)
12 Month	P=0.002 (n=631)	P=0.001 (n=631)	P=0.004 (n=542)

2.2 Effect of Outliers

Changes from baseline in erosion score at 6 and 12 months are highly skewed, with outliers in both the positive (progressed) and negative (improved) directions. This is illustrated in the following figure for changes in erosion score at 12 months.

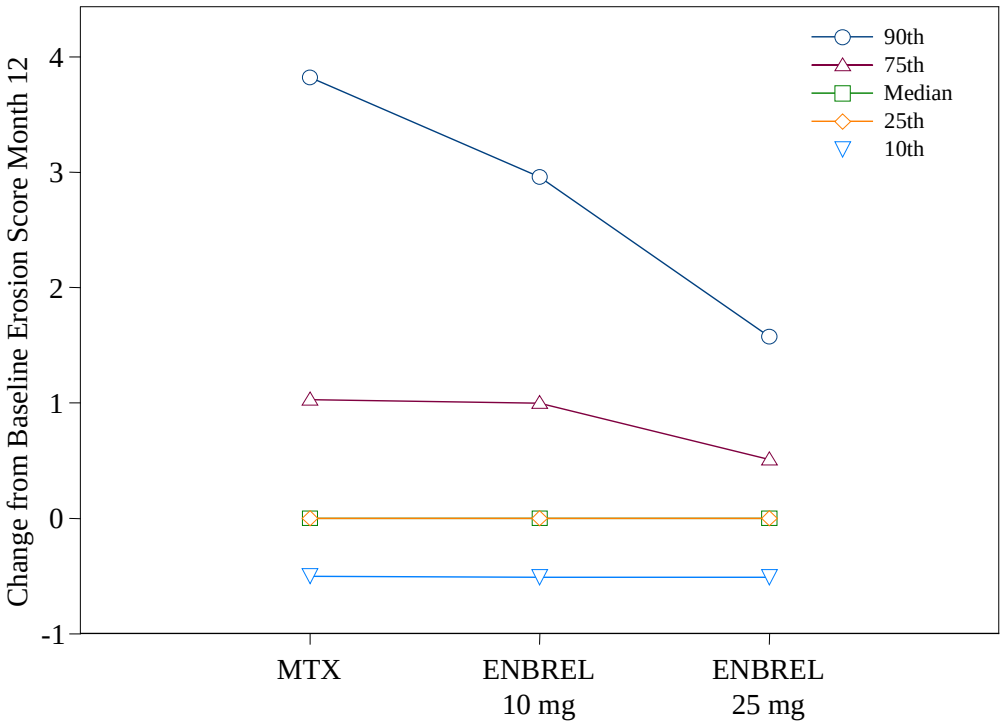


Figure 2.2A Percentiles of Month 12 Change from Baseline in Erosion Score by Treatment Group

While the non-parametric statistical analysis used to examine changes in erosion score is robust to the effect of outliers, there may still be concern that the statistically significant treatment effect is being driven by a small group of outliers distributed unequally between treatments in the two tails of the distribution. To examine the robustness of the analysis to outliers, a trimming approach was used to exclude increasing percentages of outliers from each tail (negative and positive changes in erosion score) prior to performing the comparison of Enbrel 25 mg and MTX. The following table illustrates that statistical significance of the difference in Month 12 change in erosion score is lost only when 30% of the data (subjects) are trimmed from the analysis.

Table 2.2A Results of Statistical Analyses with Trimming of Outliers

Change in Erosion Score at 12 Months

Comparison of Enbrel 25 mg and MTX

Nominal Percentage Trimmed	Number of Patients Omitted from Each Group			25 mg vs MTX p-value
		Enbrel		
	MTX	10 mg	25 mg	
0	0	0	0	0.002
2	3	9	2	0.003
10	26	21	17	0.002
20	47	46	37	0.018
30	73	66	54	0.077