BRIEFING DOCUMENT FOR ARTHRITIS ADVISORY COMMITTEE MEETING OF APRIL 11, 2000

Subject: Immunex supplemental biologic licensing application 99-0884, Enbrel for use in early rheumatoid arthritis

Prepared by: Division of Clinical Trial Design and Analysis, OTRR, CBER, FDA

TABLE OF CONTENTS

I. BACKGROUND

The current package insert for Enbrel states that "ENBREL is indicated for reduction in signs and symptoms of moderately to severely active rheumatoid arthritis and polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs)." Immunex has submitted a Supplementary Biologic Licensing Application (sBLA) to extend the indication to patients with rheumatoid arthritis with earlier stage disease who have not yet failed a DMARD. Immunex also provides data to support a claim of prevention of structural damage.

A. Previous studies

In the BLA submission for the initial approval of Enbrel for rheumatoid arthritis, Immunex submitted data from two randomized controlled clinical trials. Study I evaluated 234 subjects with active rheumatoid arthritis who had failed therapy with at least one but no more than four DMARDs and had at least 12 tender and 10 swollen joints and either an ESR of 28 mm/hr or greater or a CRP exceeding 2.0 mg/dl or morning stiffness of at least 45 min. Of the subjects who received placebo, 23% had an ACR20 response at the 3-month time point compared to 62% of subjects who received Enbrel 25 mg sc biw. Similar proportions of subjects had an ACR 20 response at 6-months. Study II evaluated 89 subjects with similar inclusion criteria except that their rheumatoid arthritis had remained active despite receiving methotrexate for at least 6 months. Of the subjects who received placebo in addition to their background methotrexate, 27% had an ACR20 response at 6 months compared to 71% of subjects who received Enbrel.

B. Guidance document for clinical development programs for products for the treatment of rheumatoid arthritis (RA)

In the document entitled "Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)," the FDA offers guidance on the conduct of clinical trials in RA. The document describes several claims, including Reduction in the signs and symptoms of RA and Prevention of Structural Damage. To support the claim of reduction in signs and symptoms, a clinical trial should be at least six months' duration unless the product belongs to an already well-characterized pharmacologic class (e.g. NSAIDs). Acceptable outcome measures include validated composite endpoints of signs and symptoms as well as well-accepted sets of signs and symptoms measures. Evidence should be provided about symptoms over time during the trial and not just at the final study visit.

In general, the guidance document is constructed to encourage sponsors to conduct longer-term studies to characterize the long-term effects of therapeutic agents for RA. Sponsors may claim benefits of their product for structural and disability outcomes, for example, only after a trial of at least one or two years, respectively, have been completed. Of note, however, the guidance document does not mandate use of any particular analysis(e.g., landmark analysis or an area under the curve (AUC)) for measuring signs and symptoms, but rather states the general notion that "in evaluating signs and symptoms, methods that evaluate response over time are preferable to methods that incorporate only the baseline value and the final observation, unless there is a reason to weight symptoms at the last visit more than intermediary symptoms."

To demonstrate prevention of structural damage, trials should be at least one year in duration. Slowing of x-ray progression may be demonstrated using a validated radiographic index such as the Larsen or the modified Sharp score. Radiographic claims should be based on comparisons of films taken at one year with those taken at baseline. All randomized patients should have films at both time points, regardless of whether they are continuing treatment.

II. CLINICAL TRIAL DESIGN AND CONDUCT

A. Initial Clinical Trial Design

Clinical trial 16.0012 is a double-blind, randomized, multicenter, active control trial comparing two doses of Enbrel, 10 and 25 mg, with methotrexate at a dose titrated from 7.5 mg to 20 mg po weekly. The trial was conducted at 69 sites in the US and Canada. A total of 632 subjects were enrolled and received at least one dose of study drug. The study specified the following inclusion criteria:

- Adult patients meeting ARA criteria for active rheumatoid arthritis
- No more than 3 years from the time of diagnosis of rheumatoid arthritis
- At least 10 swollen joints and 12 tender/painful joints

- Either ESR of at least 28 mm/hr, CRP of at least 2.0 mg/dL or morning stiffness of at least 45 min
- Positive serum rheumatoid factor or, if negative, at least three erosions present on x-rays of hands, wrists and forefeet

Patients were excluded from the study if they had:

- Previously received Enbrel, antibody to TNF or antibody to CD4
- Received intra-articular or systemic corticosteroids during the month prior to screening or the beginning of the DMARD washout period
- Significant concurrent medical diseases
- Antibody to dsDNA or to cardiolipin associated with a thrombotic event or recurrent fetal loss

The trial allowed the use of stable doses of NSAIDs and doses of oral corticosteroids up to the equivalent of 10 mg/d of prednisone as well as certain other pain medications. All subjects received folic acid 1 mg/d.

To maintain the blind in this study, all subjects received an oral drug weekly and a subcutaneous drug twice weekly. For subjects randomized to the methotrexate arm, the oral drug consisted of 2.5mg tablets of methotrexate and a subcutaneously administered placebo. For subjects randomized to receive Enbrel, an orally administered placebo in addition to subcutaneously administered Enbrel given at doses of 25 mg or 10 mg. Methotrexate was begun at 7.5 mg weekly and was increased to 15 mg weekly after 4 weeks and 20 mg weekly after 8 weeks so long as there were no symptoms of methotrexate toxicity unless the subject had no active joints. Blinded therapy was continued on all subjects until the last subject had completed 52 weeks of evaluations.

Subjects who did not achieve at least a 10% improvement in the painful/tender joint count or the swollen joint count compared to baseline were permitted to discontinue study drug and could be treated by the investigator with other DMARDs as appropriate. Such subjects remained in the study and participated in all safety and efficacy evaluations.

Radiographic assessments consisted of hand, wrist and forefoot x-rays obtained at baseline, 6 months, 12 months and 24 months. The films were digitized and read by independent radiologists who were blinded to treatment and chronologic order of films. Joint assessments were carried out by independent, blinded joint assessors.

As initially formulated, trial 16.0012 had two co-primary endpoints, a signs and symptoms endpoint and a radiographic endpoint. The radiographic endpoint was defined as a comparison of the joint erosion score at 12 months compared to baseline as measured by the modified Sharp method. The clinical co-primary endpoint was defined as a comparison of the ACR-N response area under the curve (AUC) over 6 months. The ACR-N is a measure of the overall level of response of the patient at a given time during the trial, defined by analogy with the ACR20. For example, an ACR-38 would indicate the subject had at least a 38% improvement in swollen joint counts and tender joint

counts, as well as at least a 38% improvement in 3 of the 5 additional parameters: patient global, physician global, patient assessment of pain, patient function as assessed by Health Assessment Questionnaire (HAQ), acute phase reactants.

B. Revised trial design

While study 16.0012 was ongoing, reports appeared in the literature suggesting that patients with early rheumatoid arthritis who were treated with methotrexate may have very little radiographic progression (e.g. M Maravic *et al*, J Rheum, 26, 262, 1999 and E Rich *et al*, J Rheum 26, 259, 1999). FDA raised concerns with Immunex that if the methotrexate arm of their study had very little x-ray progression, it may be difficult to demonstrate that Enbrel is effective in preventing x-ray progression by showing superiority to methotrexate.

To address the possibility that subjects with early rheumatoid arthritis treated with methotrexate may have little or no x-ray progression, Immunex revised their analysis of the x-ray endpoint such that the non-inferiority of Enbrel to methotrexate would be tested as the first analysis and, if Enbrel was demonstrated to be non-inferior to methotrexate, a second analysis testing the possible superiority of Enbrel over methotrexate would be conducted. Immunex submitted historical data to support their assumption that the expected rate of x-ray progression in untreated patients would be 6 units/year or greater based on total Sharp scores, and that the methotrexate-treated subjects would be expected to have approximately 2 units/year. Non-inferiority was tested based upon these assumptions, i.e. by statistically excluding the possibility that Enbrel was inferior to methotrexate by 1.2 units/year, or 30% of the calculated expected benefit of methotrexate [1.2 = 0.3 x (6-2)].

C. Study conduct

A total of 654 subjects were randomized in study 16.0012 (table 1). Of these, 21 subjects never received drug. These randomized-but-not-treated subjects are unlikely to be an important source of bias because they were distributed among all three arms and the reasons they were not treated were similar among the various arms of the trial. The major reasons given were that subjects did not actually meet the inclusion criteria and that the patient changed their mind about participating.

Patients who discontinued study drug before the end of the trial were encouraged to return for study evaluations for a full year. Greater than 90% of patients in all three arms of the trial had x-ray evaluations at the 12-month time point.

At the start of the trial, subjects were begun on an oral drug and a subcutaneous drug. For patients in the methotrexate arm, the oral drug was methotrexate 7.5 mg weekly. At 4 weeks, the dose of oral drug was increased to 15 mg weekly unless the subjects had a complete response with no active joints. At 8 weeks, the dose of oral drug was increased to 20 mg weekly unless the subjects had a complete response. Greater than 90 percent of subjects in all treatment arms had oral drug dosing increased to 20 mg weekly. The

median time to final dose level of oral drug was approximately nine weeks in all three of the study arms. Dosing with oral drug had to be decreased in some patients during the trial because of toxicity. The proportion of subjects remaining on maximum oral drug dose at 52 weeks was lower in the methotrexate arm than in the two Enbrel arms.

Approximately 80% of study subjects completed 12 months of dosing on blinded study drug in the three study arms, with a somewhat higher proportion of subjects completing dosing in the Enbrel 25 mg arm than in the methotrexate arm. The reasons for not completing 12 months of dosing are shown below in table 1. The most common reasons for not completing the full 12-month course included adverse events and lack of efficacy meeting pre-specified criteria. A higher number of subjects dropped out for adverse events in the methotrexate arm than in the Enbrel arms. The most common adverse events leading to dropout were toxicities which have been associated with methotrexate, including alopecia, oral/nasal ulcers, and vomiting, as well as infection. The adverse events leading to dropout are discussed in more detail below in the section on safety.

Table 1. Patient disposition

Patients enrolled: 654			
	MTX	Enbrel 10 mg	Enbrel 25 mg
Patients randomized, but not treated	7	5	9
Received ≥1 dose: modified ITT population	217 (97%)	208 (98%	207 (96%)
Completed 12 month evaluation	202 (93%)	188 (90%)	193 (93%)
Received maximal oral drug dose (MTX or placebo), i.e. 20 mg/wk	94%	93%	91%
Receiving max. oral drug dose at 52 wks	77%	87%	89%
Median time to final dose level (wks)	9	9	9
Completed 12 months dosing	79%	80%	85%
Reasons for not completing:			
AE	21	9	10
Abnormal labs	3	3	3
LOE per protocol	8	13	9
Refusal	6	8	4
Protocol violations	4	3	1
Lost to follow-up	1	2	1
Other	2	2	1

AE= adverse event

LOE= lack of efficacy

The study protocol mandated reduction of dosing of oral study drug in the event of toxicity. A larger proportion of subjects randomized to the methotrexate arm required dose reduction of oral drug than in the two Enbrel arms. The most common reasons for dose reduction were adverse events, and elevated liver enzymes (table 2).

Table 2: Dose Reductions of Oral Study Drug

	MTX N = 208	Enbrel 10 mg N = 208	Enbrel 25 mg N = 207
No. (%) of patients with dose reductions	32 (15%)	8 (4%)	4 (2%)
Reasons for dose reduction:			
AEs:	17 (8%)	3 (1%)	2 (1%)
Nausea + dyspepsia or headache or asthenia	8 (4%)	3 (1%)	2 (1%)
Oral ulcer +stomatitis or diarrhea	5 (2%)	0 (0%)	0 (0%)
Diarrhea	1 (<1%)	0	0
Alopecia	2 (1%)	0 (0%)	0 (0%)
CHF (suspected pneumonitis)	1 (<1%)	0 (0%)	0 (0%)
Elevated LFTs	16 (7%)	4 (2%)	1 (4%)
Other	0 (0%)	1 (<1%)	1 (<1%)

D. Patient population

The baseline characteristics of the patient population in the three arms of the trial are given in table 3. The three arms appeared balanced with respect to age, ethnicity, duration of disease, rheumatoid factor positivity and use of corticosteroids. The mean age for this population was 50. Approximately 75% were female. The mean duration of disease was 12 months. Time of disease onset (greater or less than eighteen months from study initiation) was defined as a stratification variable for the study. No patient with disease onset greater than 3 years from study initiation was enrolled into the study. Three-quarters of subjects experienced disease onset within eighteen months of study initiation (0-18 mo), and one-quarter experienced disease onset within 18-36 months of study initiation..

Table 3: Baseline demographics

	All Patients		
	MTX	Etanercept	
		10 mg	25 mg
	N=217	N=208	N=207
Mean age (years)	49	50	51
Age range	21-80	19-84	21-82
Age ≥65 years (%)	15	14	18
Female (%)	75	75	74
Caucasian (%)	88	84	86
Mean weight (kg)	76	78	79
RA duration (months)[a]			
mean	12	11	12
median	8	7	8
Stratification (n/%):			
<18 months	163 (75)	158 (76)	157 (76)
18-36 months	54 (25)	50 (24)	50 (24)
Rheumatoid factor positive	89	88	87
Any prior DMARDS (%)	46	39	40
Mean no. prior DMARDs	0.6	0.5	0.5
DMARDs at washout (%):			
any	24	25	23
hydroxychloroquine	16	20	15
Concomitant therapy at BL (%)			
NSAIDs	80	76	86
corticosteroids	41	42	39
Mean daily dose in pts. receiving corticosteroids (mg)	7	7	9

E. Protocol modifications

As is stated above, after the clinical trial had begun, reports were published in the literature suggesting the possibility that many patients with early rheumatoid arthritis treated with methotrexate would develop few, if any, erosions. For example, Rich et al. (*J Rheum, 26:259-261, 1999)* reported in a group of 24 patients who were treated with methotrexate as their first DMARD that half of all patients showed no progression. The majority (83%) of these patients were rheumatoid factor positive. The agency and Immunex discussed concerns that it might be difficult to demonstrate the efficacy of Enbrel in delaying radiographic progression based on superiority to methotrexate if the methotrexate arm showed little or no radiographic progression.

Under certain circumstances, efficacy of a new therapy can be established by demonstrating equivalence, or non-inferiority, to a known effective agent, rather than by demonstrating superiority to a comparator arm. To assess the efficacy of Enbrel in delaying radiographic progression in the event that the methotrexate arm showed little or no progression, Immunex proposed revising the analysis of the radiographic endpoint to non-inferiority to methotrexate rather than the originally specified analysis of superiority. In the revised analytic plan, a sequential design was proposed where first non-inferiority

would be tested then, if successful, superiority would be tested. Immunex submitted clinical trial data to calculate an expected rate of progression in untreated patients and an expected rate of progression for patients receiving methotrexate. These measures were used to calculate an expected effect size for methotrexate. In a non-inferiority trial, a margin is specified to indicate a degree of inferiority (delta) that must be excluded for the test drug to be deemed non-inferior to the active control. The analytic plan was revised to state that Enbrel would be deemed equivalent to methotrexate if Enbrel could be demonstrated to be no more than 30% inferior (95% one-sided confidence interval) to the assumed effect size for methotrexate. Historical data supporting the assumed effect of methotrexate in this population are shown below. Both the sponsor and the agency were well aware of the uncertainties involved in the use of non-inferiority studies to demonstrate efficacy of new agents in delaying radiographic progression, especially uncertainties in determining an assumed effect size for methotrexate in this population of patients. The historical database is not entirely clear in this regard, for there are differences in the patient populations studied in this protocol compared to the studies used to establish the effect size for methotrexate. However, given rapid changes in the development of therapeutic agents for rheumatoid arthritis, and given increasing concerns in the clinical community regarding the merits and ethics of studies using placebo controls for long durations, these limitations were deemed acceptable by the sponsor. Both the agency and the sponsor recognized, however, that an unequivocal determination of the benefits of Enbrel in delaying structural damage may be difficult with certain data outcomes given that the assumptions used for estimating the benefits of methotrexate were somewhat problematic. It was made clear to the sponsor, therefore, that a careful evaluation of all trial data, including a number of secondary endpoints, would be critical for any determination of efficacy for structural outcomes.

F. Review of Historical Literature

In order to test the efficacy of a novel therapy based on equivalence to a positive control therapy, it is necessary to specify:

- The expected result in untreated patients;
- The expected degree of benefit associated with treatment with the positive control;
- The effect size for the positive control treatment; and
- The margin of inferiority to be excluded.

To estimate the rate of radiographic progression in untreated rheumatoid arthritis patients, Immunex submitted the results of a study by Wolfe et al. (Wolfe F and Sharp JT, Arthritis & Rheumatism, 41, 1571-1582, 1998) which followed 256 patients with rheumatoid arthritis first seen within the first two years of disease. Approximately 74% of the patients were rheumatoid factor positive. The mean age was 52 years. Seventy-three percent were female. The ESR at baseline was 40 mm/hr. The mean level of disability based on the HAQ was 0.89 at baseline. Patients had used a variety of anti-

rheumatic drugs prior to the first clinic visit including auranofin, IM gold, hydroxychloroquine and prednisone. During follow-up of up to 19 years, 78% of all patients used a DMARD. The most common DMARDs used were methotrexate, hydroxychloroquine, IM gold and auranofin. Forty percent used prednisone at one time or another during the trial. Radiographs were to be obtained every two years. Of 583 patients from this study (having inclusion criteria specifying a disease duration of less than two years at initial visit), 256 had at least two paired radiographs. The mean rate of radiographic progression based on the total Sharp score was 4.5 u/yr ± 4.9 (SD). The median total Sharp score was 3.1. The mean annual change in erosion score for all patients was 1.9 ± 2.5. The mean rate of radiographic progression, based on the total Sharp score, was approximately 4.5 u/yr in patients with one year of disease. This rate fell to approximately 3.5 units per year for patients with disease of 8-10 years duration, but was higher for patients with a disease duration longer than twelve years. Since most of the patients in this observational study were receiving DMARD's, it is impossible to determine how much radiographic progression they would have had if they had been untreated. If the DMARD's they took retarded their x-ray progression, then the rate expected for untreated patients might be higher.

Immunex also submitted data from two trials conducted for licensure of ARAVA to provide estimates of the rate of radiographic progression in untreated patients. In one of these trials, MN301/303, the placebo-treated patients experienced a rate of radiographic progression of 5.6 Sharp score units per year. In the other study, US 301, the placebo patients had a rate of radiographic progression of 2.2 units per year. However these patients were allowed to cross over to active treatment during the course of the year of observation.

To provide evidence that methotrexate delays x-ray progression, Immunex cited several studies in the literature as well as the study described in the label for ARAVA. In that study (US 301), patients treated with ARAVA had significantly less radiographic progression based on the Sharp score than patients in the placebo group. In addition, patients treated with methotrexate also has significantly less x-ray progression than patients treated with placebo.

In conclusion, one study was cited by the sponsor which measured radiographic progression rates in untreated and methotrexate-treated patients using the same study, namely the US301 study. This study found a rate of radiographic progression of 5.6 u/yr for the total Sharp score in the placebo patients and 2.2 u/yr in the methotrexate arm, indicating an effect size of 3.4 u/yr. The US301 study did not study the same early-stage RA patient population as that enrolled in the current Immunex study. The sponsor also cited a large observational trial (Wolfe and Sharp), but this study measured radiographic progression in neither untreated patients nor in a group treated uniformly with methotrexate. Therefore, the Wolfe and Sharp study cannot provide precise figures on effect size for methotrexate's effects on radiographic progression.

Based on the above data, Immunex estimated that the rate of radiographic progression expected in their patient population if they had been untreated was approximately six

units per year. They estimated an expected rate of radiographic progression in methotrexate-treated patients of 2 u/yr. Therefore, the effect size was 4 u/yr (6 - 2 u/yr). The margin was set at 30 percent of the effect size, or 1.2 u/yr. The primary analysis stated that non-inferiority would be demonstrated if the 95% confidence intervals around the difference between the methotrexate arm and Enbrel arm excluded an inferiority of 1.2 units or greater.

G. Reading of radiographs

Hand and foot radiographs were obtained on subjects at baseline, at 6 months and at 12 months. Immunex employed several methods to maintain a consistent quality of films including use of an x-ray acquisition manual, use of the same film for all radiographs for the study, and a review of the films shortly after acquisition. Repeat films were requested as needed. Films from the 1749 patient time points (2 films per time point: hands, and feet) were read by six trained readers in a blinded, random order. Each film was read by at least two readers. To assess inter- and intra-reader reliability, 10% of subjects had films read by all 6 readers. The coefficient of variability ranged from 0.8 to 0.9.

The agency reviewed the radiographs and the assessment of the blinded readers. Radiographic data in the submission was complete and of uniformly good quality. The readings by the blinded readers were generally consistent and accurate.

III. EFFICACY ANALYSIS

A. Co-Primary endpoint: Radiographic endpoint

The primary endpoint specified in the study was a comparison of the mean annual change in total Sharp score. The mean change in the total Sharp score was calculated using a mixed model which took into account the baseline, 6-month and 12-month radiographs, as well as baseline covariates. The distribution of the data is shown in appendix I. As shown in figure 1, the patients in the methotrexate arm experienced a mean increase in total Sharp score of 1.3 u/yr. The mean change in total Sharp score in the Enbrel 25 mg arm was 0.8 u/yr. The difference between the Enbrel 25 mg arm and methotrexate arm was therefore minus 0.5. The 95% confidence interval around this difference excluded the difference of 0.2 units, thereby excluding the prespecified margin of inferiority of 1.2 units or greater. After excluding a non-inferiority of 1.2 units or greater, the sequential analysis described in the protocol next specified a test of superiority. A statistical test for superiority of Enbrel 25 mg to the active control did not reach statistical significance ($p = 0.21$).

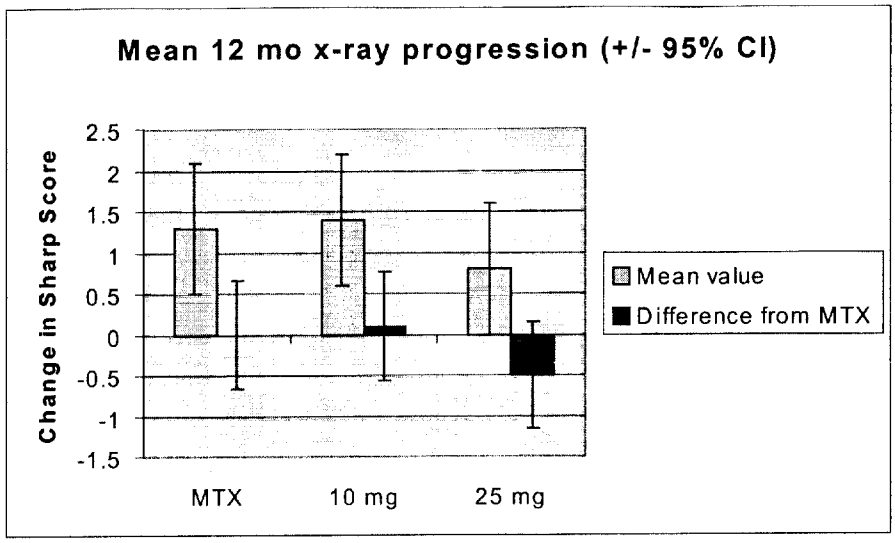
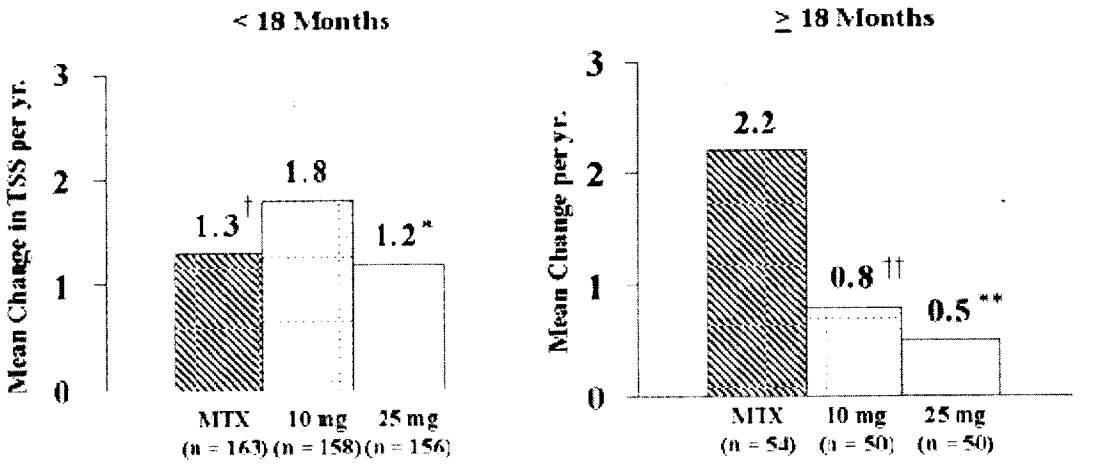


Figure 1. Primary radiographic endpoint

The protocol stratified subjects based on the duration of disease, i.e. 0-18 mo vs. 18-36 mo. Analysis of the annual change in total Sharp score in the group with longer duration of disease showed a statistically significant difference between methotrexate and Enbrel 25 mg (figure 2)



† upper-limit 1-sided 95% CI, 10 mg - MTX = 1.30
* upper-limit 1-sided 95% CI, 25 mg - MTX = 0.66

†† upper-limit 1-sided 95% CI, 10 mg - MTX = -0.11
** upper-limit 1-sided 95% CI, 25 mg - MTX = -0.39

Figure 2: Analysis of annual change in total Sharp score by disease duration

Limitations of non-inferiority analysis

As discussed above, use of a non-inferiority endpoint to demonstrate efficacy of a novel therapy requires knowing the expected effect size for the active control in the patient population under study. The sponsor submitted data to support the effect of methotrexate in delaying radiographic progression, but these data were obtained using a patients differing significantly from those studied in the current trial both with respect to duration of disease and with respect to prior DMARD use. Extrapolating the data from these other trials to determine an expected effect size for methotrexate in the current trial require making assumptions whose validity cannot be directly demonstrated. Thus, although the study ruled out that Enbrel was inferior to methotrexate by a margin exceeding 1.2 u/yr, uncertainties about the assumptions used in the analysis led the agency to closely examine additional data supporting the efficacy of Enbrel for delaying radiographic progression.

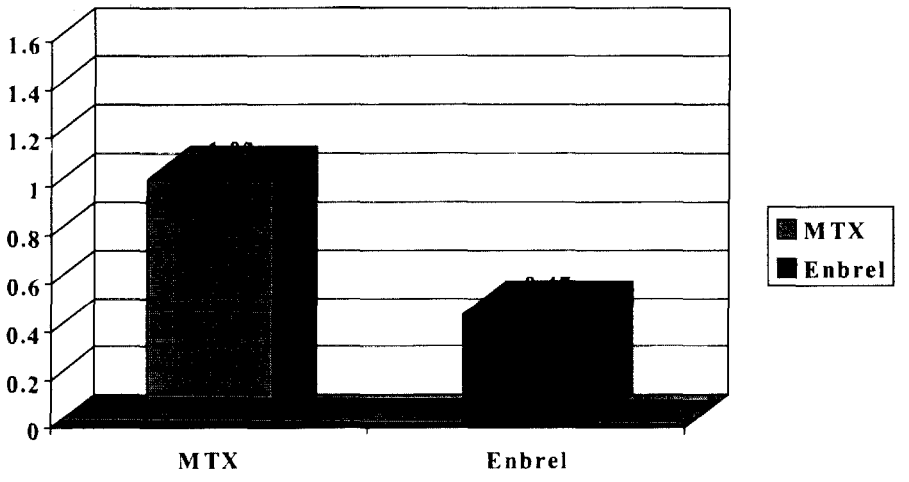


Figure 3. 12 mo change in erosion scores

Originally specified primary endpoint

The total Sharp score is derived by combining two components: the erosion score and a measure of joint space narrowing. The primary radiographic endpoint in the original protocol was a comparison of the 12-month change in erosion score. When Immunex changed the primary analysis to a non-inferiority trial, the primary endpoint was changed to the total Sharp score, because data were not available to estimate the effect size for methotrexate for erosion scores. The prespecified analysis for the original primary endpoint of erosion score was a comparison of means using the mixed model. For its analysis of the original primary endpoint, the agency used the last value for erosion score minus the baseline value and adjusted for the time interval. For the agency's analysis, a non-parametric test of statistical significance was used because the data were not normally distributed. The 12-month change in erosion score was decreased in the Enbrel 25 mg arm compared to methotrexate using the originally specified mixed model (0.4 vs. 0.9 u, p=0.047). Using the agency analysis, the 12-month change in erosion score was also decreased in the Enbrel arm compared to the methotrexate arm (0.47 u vs 1.03 u, p=0.0013). No differences were seen between Enbrel and methotrexate with respect to 12-month changes in joint space narrowing (0.4 u for both methotrexate and Enbrel 25 mg using the mixed model, p=NS). The 12-month change in erosion score was lower in

the Enbrel-treated subjects in both of the two prespecified disease duration strata (figure 4).

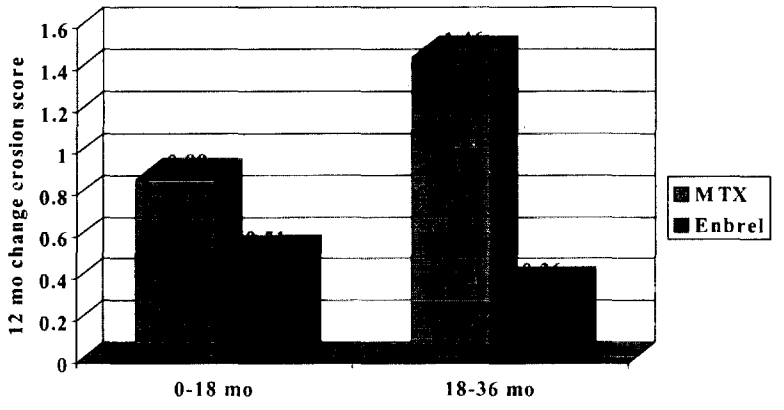


Figure 4. 12-month change in erosion score, subsetted by duration of disease

Secondary analyses of radiographic data.

To determine whether there were differences in the degree of radiographic progression in the first part of the study compared to the latter part, changes in the radiographic endpoints in the first 6 months of the trial were compared. The 6-month change in total Sharp score was decreased in the Enbrel 25 mg arm compared to methotrexate (figure 5, $p = 0.0006$). In the 6 to 12 month period, the degree of change in total Sharp score was lower in both arms of the trial, but the difference between the two arms was considerably less. When the erosion score component of the Sharp score is considered separately, the mean change in the first six months was similarly decreased in the Enbrel 25 mg arm compared to methotrexate (figure 6, $p= 0.0006$). The amount of change in erosion score was less in both the Enbrel 25 mg arm and the methotrexate arm in the second six months compared to the initial 6 months of the trial.

To assess stabilization of radiographic progression, subjects were assessed whose change in Sharp score during the trial was zero or negative. The proportion of subjects with no radiographic progression was higher in the Enbrel 25 mg arm than the methotrexate arm for the first 6 months of the trial with respect to both the total Sharp score and the erosion

score (Figure 7, p = 0.004 and 0.0006, respectively). At 12 months, the proportion of subjects with no radiographic progression based on erosion scores was less in the Enbrel-treated subjects than in the methotrexate arm, while the proportion of subjects with no change in total Sharp score at 12 months was also lower but did not reach statistical significance (p = 0.004 and 0.17, respectively).

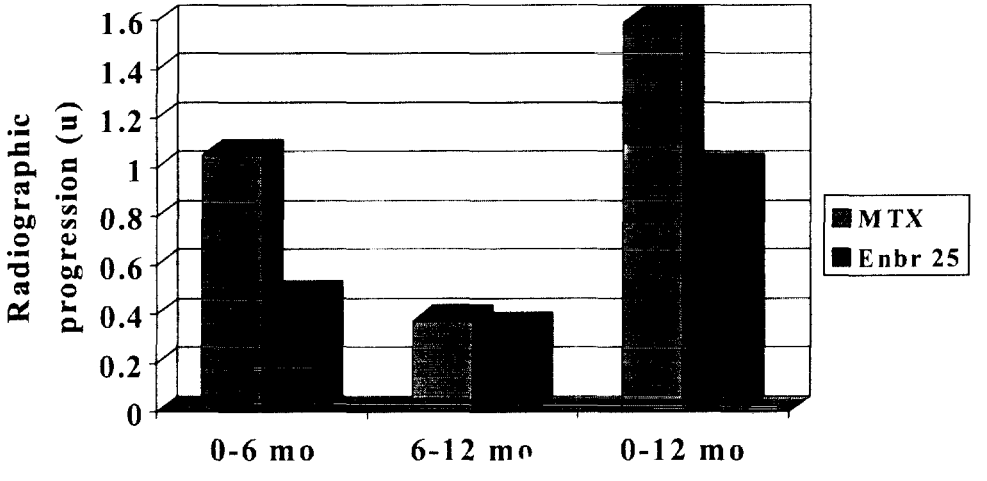


Figure 5. Change in total Sharp score over time

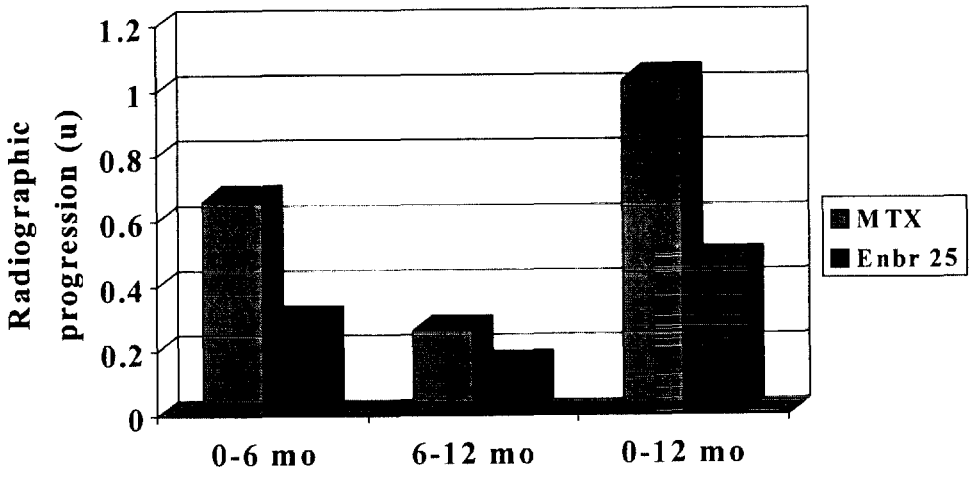


Figure 6. Change in erosion scores over time

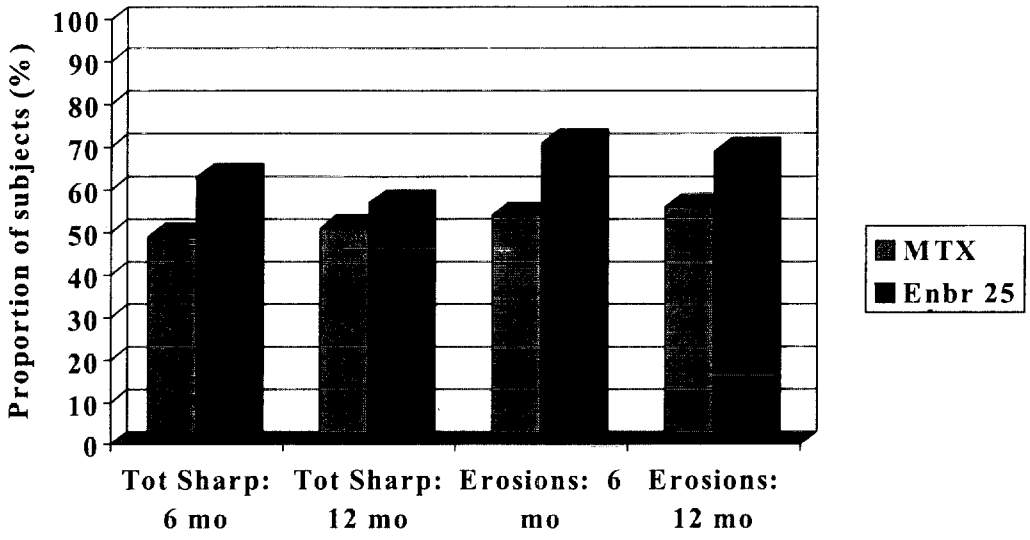


Figure 7. Subjects with no radiographic progression

Subset analysis

The 12-month change in erosion scores was compared in the methotrexate arm and the Enbrel arm among subjects subsetted based on age, their ethnicity and gender. Approximately, one-quarter of all subjects were aged 60 or older. The subjects younger than age 60 who received Enbrel 25 mg had lower changes in erosion scores than those receiving methotrexate (figure 8). Among subjects 60 or older, the change in erosion score was higher among receiving Enbrel 25 mg than those receiving methotrexate, but the difference was not statistically significant (p=0.31). Approximately one-quarter of all subjects were male. Similar decreases in erosion scores were seen among males and females receiving Enbrel compared to those receiving methotrexate. Approximately 86% of subjects were Caucasian, while 6% were Hispanic, 5% Black and 2% Asian. Erosion scores were lower in the Enbrel-treated subjects than in those receiving methotrexate in all ethnic groups.

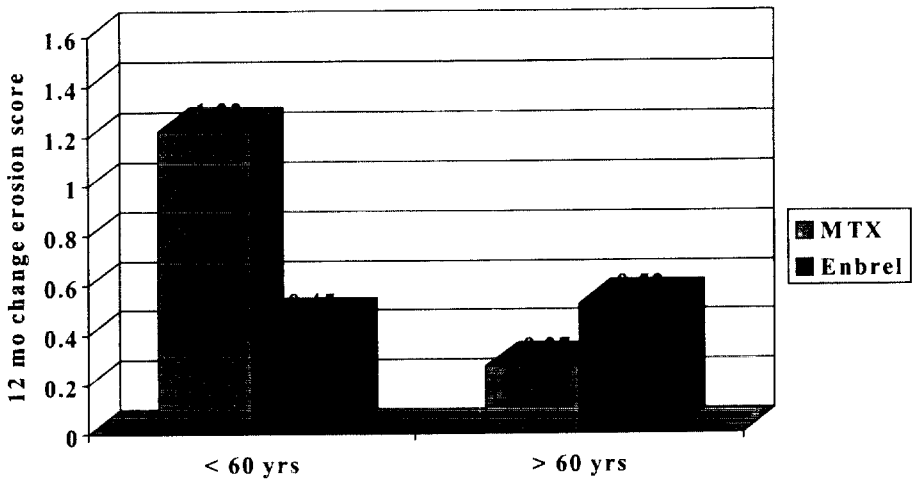


Figure 8. Erosions scores in subjects subsetted by age

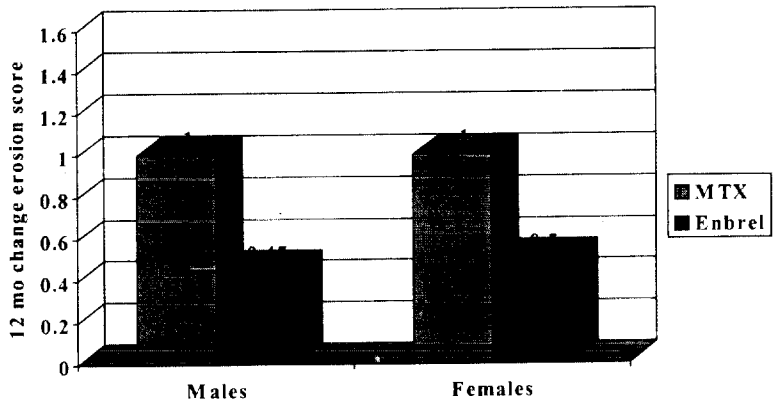


Figure 9. Erosions scores in subjects subsetted by gender

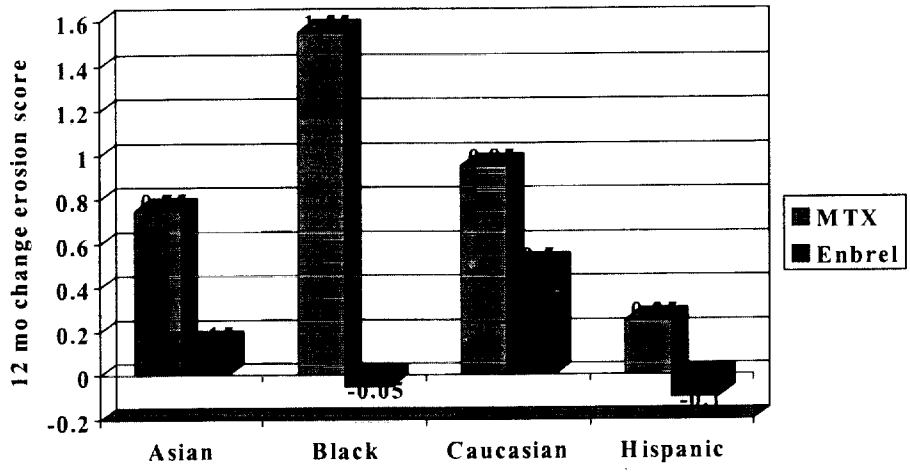


Figure 10. Erosion scores in subjects subsetted by ethnicity

Elevation in acute phase reactants and signs of erosions on x-rays are considered to have prognostic significance in rheumatoid arthritis. For this reason, subjects were evaluated separately based on the presence or absence of erosions at baseline and on the presence or absence of elevated ESR. The 12-month change in erosion scores was decreased among both those with 2 or more erosions at baseline as well as those with fewer than 2 erosions at baseline (figure 11). To assess subjects with an elevated ESR at baseline, a high value was defined as an ESR exceeding 30 mm/hr. Approximately 56% of all subjects had an ESR of 30 mm/hr or greater at baseline. The 12-month change in erosion score was lower in Enbrel-treated subjects compared to methotrexate-treated subjects among subjects with elevated baseline ESR as well as those with baseline ESR below 30 mm/hr (fig 11).

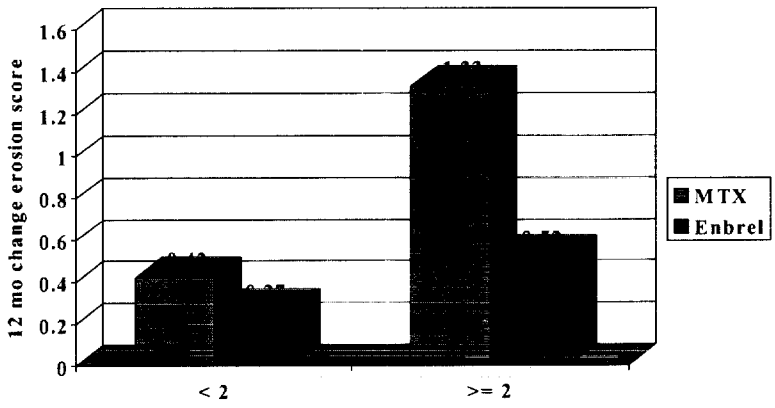


Figure 11. Erosions scores in subjects subsetted by baseline erosion scores

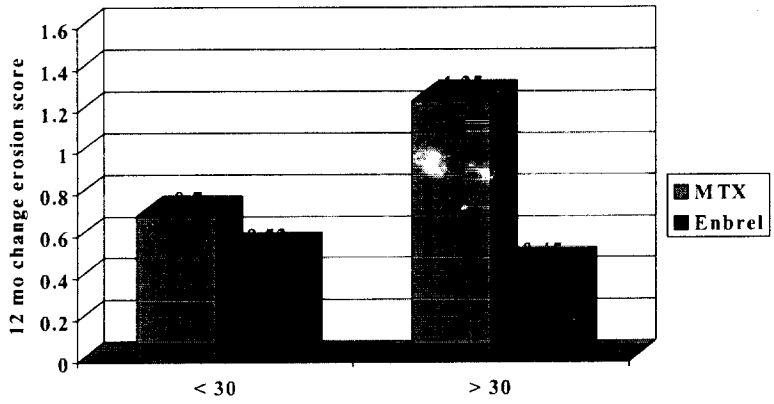


Figure 12. Erosions scores in subjects subsetted by baseline ESR (< 30 mm/hr vs. 30 mm/hr or greater)

Summary of radiographic data

Based on the specified radiographic endpoint of 12-month change in total Sharp score, the 95% confidence intervals exclude that Enbrel was more than 1.2 u/yr inferior to methotrexate. However, because of uncertainties estimating the effect size for methotrexate in the current trial, a demonstration of non-inferiority alone may not be adequate to establish the efficacy of Enbrel in delaying radiographic progression. Additional data supporting activity of Enbrel in delaying radiographic progression include the original primary endpoint of 12-month change in erosion scores, which was decreased in Enbrel-treated subjects compared to those receiving methotrexate. In addition, analysis at 6 months showed decreases in both erosion scores and total Sharp scores for the Enbrel-treated subjects. No subset was found where erosion scores were significantly worse among Enbrel-treated than methotrexate-treated subjects.

B. Co-Primary endpoint: Signs & Symptoms

The co-primary endpoint for this trial was signs & symptoms as measured by the area under the curve (AUC) for a measure called the ACR-N for the first 6 months of the trial. As described above, the ACR-N for a subject at a particular point in time is a measure of their overall level of improvement based on the same components as the widely-used ACR20 measure of improvement. As an example, an ACR-N of 38 indicates that a subject has at least a 38% improvement in swollen joint count and tender/painful joint count as well as at least a 38% improvement in patient global assessment, physician global assessment, patient assessment of pain (by VAS), patient function (HAQ) and acute phase reactants. The ACR-N achieved over time by subjects in the methotrexate arm and the Enbrel 25 mg arm is shown in figure 13. The difference between the level of response in the two arms is greatest in the first few months of the trial, however the mean ACR-N for the Enbrel 25 mg arm remains higher than that for the methotrexate arm throughout the trial. There was a statistically significant difference in the AUC for the ACR-N for the first 6 months of the trial (15.3 for Enbrel 25 mg, 13.0 for Enbrel 10 mg, 11.5 for methotrexate, $p = 0.006$). A significantly greater degree of improvement was experienced by subjects in the Enbrel 25 mg arm compared to the methotrexate arm ($p = 0.002$).

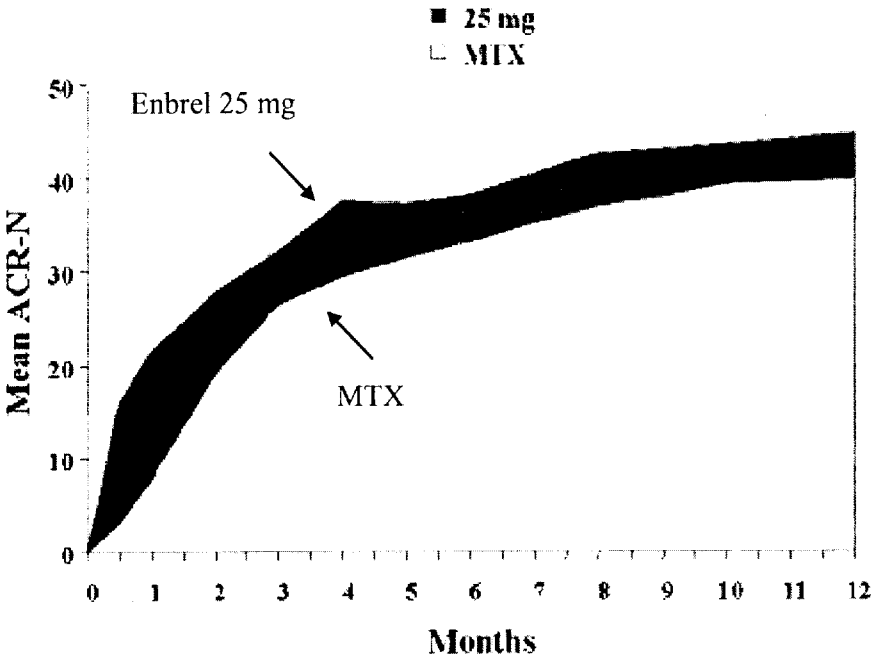


Figure 13. ACR-N over time during the study

The proportion of subjects achieving an ACR 20, 50 and 70 at various points during the trial is shown in table 4. Although the proportion of subjects with an ACR 20 and 50 were somewhat higher in the Enbrel 25 mg arm than the methotrexate arm at the 6 month and 12 month time points, the differences were not statistically significant. A higher proportion of subjects in the Enbrel arm attained an ACR 70 at 3 months compared to the methotrexate arm (13% vs. 7%), however the difference between treatment arms was less at 12 months (25% vs. 22%).

Table 4. ACR 20, 50 and 70 responses at 3, 6 and 12 months

	MTX	Etanercept	
		10 mg	25 mg
	N = 217	N = 208	N = 207
Time	N (%)	N (%)	N (%)
20% ACR			
Month 3	116 (56)	108 (53)	123 (62)
Month 6	121 (58)	115 (59)	130 (65)
Month 12	129 (65)	115 (61)	138 (72)
50% ACR			
Month 3	50 (24)	56 (28)	57 (29)
Month 6	67 (32)	64 (33)	79 (40)
Month 12	85 (43) †	61 (32)	95 (49)**
70% ACR			
Month 3	15 (7)	16 (8)	26 (13)*
Month 6	28 (14)	26 (13)	42 (21)*
Month 12	44 (22)	31 (16)	49 (25)

C. Other analyses

Functional assessment

The level of disability was assessed at baseline and during the trial by use of the Health Assessment Questionnaire (HAQ), which assesses patients on a 0 (no disability) to 3 (maximum disability) scale. At baseline, the three arms were well-balanced. All three arms showed patients having HAQ scores of approximately 1.45. The level of disability was lower in all three treatment arms at 12 months than at baseline. The differences between treatment arms was not statistically significant.

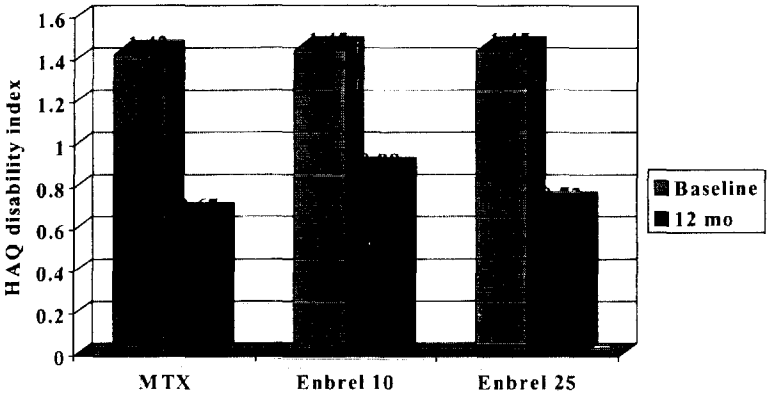


Figure 14. Disability as measured by the Health Assessment Questionnaire (HAQ)

Health-Related Quality of life

Health-related quality of life was assessed using the SF-36 questionnaire at baseline and at various timepoints during the trial. The SF-36 measure consists of 8 subdomains spanning various aspects of health-related quality of life: physical functioning (PF), role limitations attributable to physical problems (RP), bodily pain (BP) and general health (GH), role limitations attributable to emotional problems (RE), social functioning (SF), vitality (VT) and mental health (MH). The scores on the subdomains can be summarized in terms of two summary scores: the physical component summary score (PCS) and a mental component summary score (MCS). The PCS is derived from weightings from all the subdomain scores with the largest weight contributed by the four subdomains most closely associated with physical function, i.e. physical functioning (PF), role limitations attributable to physical problems (RP), bodily pain (BP) and general health (GH). In contrast, the MCS derives its largest contributions from the four subdomains most closely associated with mental function, i.e. role limitations attributable to emotional problems (RE), social functioning (SF), vitality (VT) and mental health (MH).

The scores for the subdomains and the summary scores can be expressed either as raw scores or as normalized scores, based on scores from the US population as a whole. Immunex expressed scores for this trial as norm-based scores, where the US population norm is 50 units for each measure and the standard deviation is ± 10 units. At baseline, the scores for both the PCS and the MCS were well balanced among the three treatment arms (figures 15-16). Scores for the PCS at baseline were 28-29 units, approximately two

standard deviations below US population norms. Baseline scores for the MCS were 46-47, just slightly below US population norms.

The protocol-specified endpoint for health-related quality of life was the 12-month change in the PCS. At the 12 month timepoint, scores on the PCS were higher in all treatment arms compared to baseline. There was an increase of 10.7 units in the PCS for the Enbrel 25 mg arm, 9.6 units for the methotrexate arm and 6.6 units for the Enbrel 10 mg arm. The global comparison among treatment arms was statistically significant ($p = 0.008$). A dose-dependent increase in PCS scores was seen with improvement in the Enbrel 25 mg arm significantly greater than the Enbrel 10 mg arm ($p = 0.002$). The difference between methotrexate and Enbrel 25 mg did not reach statistical significance ($p = 0.27$).

As described above, scores for the MCS at baseline were only slightly below US norms. Scores on the MCS were higher at 12 months than at baseline in all arms of the trial. There were no statistically significant differences among treatment arms. The mean change from baseline for each of the subdomains is shown in figure 17.

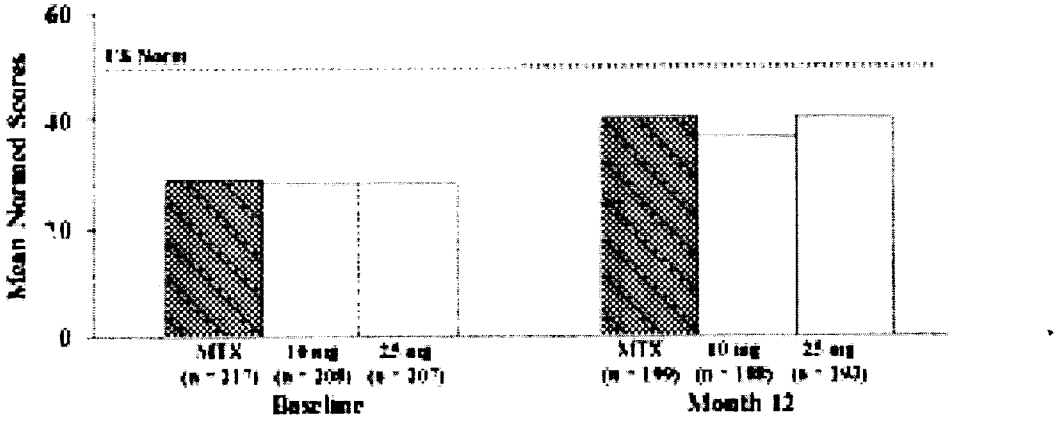


Figure 15. Health-related quality of life: SF-36 physical component (PCS)

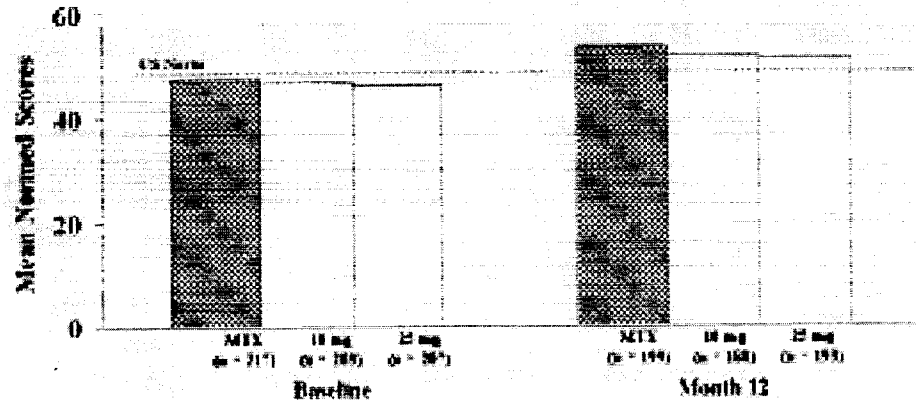


Figure 16. Health-related quality of life: SF-36 mental health component (PCS)

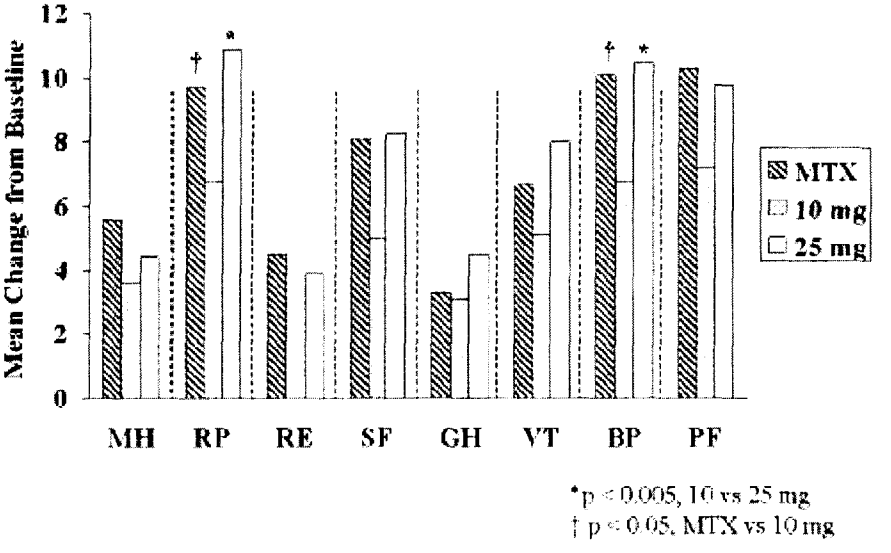


Figure 17. Health-related quality of life: Mean change from baseline in SF-36 subscales at month 12. The p values given are nominal p values for the pairwise comparisons

Major clinical response

The RA guidance document provides criteria to define a clinical response which is large in magnitude and is sustained for at least 6 months, called a Major Clinical Response. The definition of a Major Clinical Response utilizes the ACR70 because a 70% improvement is rarely, if ever seen in the placebo arms of randomized clinical trials of RA. A subject with a Major Clinical Response is thus defined as a subject who attains an ACR70 which is maintained for 6 consecutive months with no measurement falling below an ACR70 during that time.

Patients were seen in the trial who met criteria for a Major Clinical Response. Overall, 11% of all subjects in the Enbrel 25 mg arm, 5% in the Enbrel 10 mg arm and 8% in the methotrexate arm achieved a Major Clinical Response. The differences in global comparison of treatment arms (the prespecified analysis) were not statistically significant ($p = 0.058$).

VI. SAFETY ANALYSIS

A. Summary

Enbrel has been prescribed to an estimated 65,000 patients with rheumatoid arthritis since licensure in November, 1998. Although data from controlled clinical trials and long-term open-label studies indicated that Enbrel was generally safe and well tolerated, in the months following licensure, reports of deaths from serious infection and sepsis were received by the agency. In response to these reports, Immunex issued a Dear Doctor letter calling for caution in the use of Enbrel in patients who may be at increased risk for infection. Immunex is currently in the process of conducting a controlled clinical trial in 1000 patients to assess the safety of Enbrel use in patients with conditions which may predispose to serious infections.

In the current trial (16.0012), serious adverse events (SAEs) were observed at a similar rate overall in the Enbrel 25 mg arm and the methotrexate arm. Thromboembolic events were observed more frequently in the Enbrel-treated subjects than in those receiving methotrexate, while interstitial pneumonitis was observed only in the methotrexate arm. A similar number of infectious SAEs were observed in the Enbrel 25 mg arm and the methotrexate arm. A higher proportion of subjects in the methotrexate arm discontinued treatment due to toxicity. The most common cause for discontinuation was adverse events which have been previously associated with the use of methotrexate.

Immunex is in the process of conducting a 1200-subject, 3-year, open-label trial to assess the safety of long-term use of Enbrel in rheumatoid arthritis. At present, 573 subjects have been treated for 1-3 years. No adverse events have been observed to date with a higher incidence with increased duration of exposure to Enbrel.

B. Summary of post-marketing reports

In the five months following licensure of Enbrel, the agency received reports of 30 serious infections, including 6 deaths, out of an estimated 25,000 rheumatoid arthritis patients who were receiving Enbrel therapy. Analysis of these reports indicated that a large proportion of cases occurred in patients with one or more potential risk factors for serious infections: diabetes mellitus, active infection at the time of initiation of Enbrel, and a history of chronic or recurrent infections. Concern was raised that Enbrel, by inhibiting TNF, an important arm of host defenses, may impair the ability of certain predisposed patients to fight serious infections.

In response to the reports of serious infections, Immunex issued a Dear Doctor letter reporting the cases of serious infection and announcing an addition to the package insert:

- Stating that therapy should not be initiated in patients with active infection;

- Recommending caution in prescribing Enbrel to patients with chronic or recurrent infections or with underlying conditions such as advanced or poorly controlled diabetes that may predispose them to infections

The reports of serious infection raised the question of whether patients with underlying conditions predisposing them to infection may be at higher risk when receiving Enbrel. However, controlled clinical trial data have not demonstrated an increase in the number of serious infections. In addition, the 26 non-insulin requiring diabetic patients who received Enbrel in clinical trials did not have a higher incidence of infections. Finally, many patients who developed serious infections while receiving Enbrel in clinical trials had outcomes no different from patients in the control arms. To address the issue of whether Enbrel increases the risk of serious infection in certain patients, Immunex agreed on the design of a clinical trial with the agency to assess the safety of Enbrel in patients with underlying conditions which predispose them to infection. The trial is a randomized, placebo-controlled, 4-month trial of 1000 subjects with comorbid disorders including diabetes requiring insulin or oral hypoglycemic agents, chronic pulmonary disease (COPD or asthma), a history of pneumonia in the past year or a history of recurrent bronchitis, sinusitis or urinary tract infection (at least 2 episodes in the past year). The trial will be closely monitored by a data safety monitoring board and will be terminated early if there is evidence for a safety concern.

C. Deaths and serious adverse events

During the course of trial 16.0012, two deaths occurred. There was one death of lung cancer in a subject in the Enbrel 10 mg arm diagnosed after two months of dosing. The other death was in the Enbrel 25 mg arm and arose from non-infectious complications of an aortic aneurysm repair.

The serious adverse events (SAEs) occurring during trial 16.0012 are shown in table 5. The most commonly occurring SAE was infections, followed by malignancies, thromboembolic events (DVT and pulmonary embolus), interstitial pneumonitis, angina/acute MI. The SAEs which were not included in the above categories are:

- MTX: hysteria (conversion reaction), liver function abnormality, hypertension (secondary to pneumonia), skin carcinoma (non-melanoma skin cancer), cholelithiasis, accidental injury, spontaneous bone fracture, arthralgia and emotional lability
- Enbrel 10 mg: urinary retention, depression, CVA
- Enbrel 25 mg: vascular anomaly (dissecting aortic aneurysm), GI hemorrhage, colitis (diverticulosis of the colon), depression, back pain, abdominal pain, CVA and atrial fibrillation

The most common type of SAE in the trial was infections. The infectious SAEs observed are shown in table 6. Pneumonia was seen in 3 subjects in the MTX arm, 3 in the Enbrel 25 mg arm and 1 in the Enbrel 10 mg arm. Sepsis or bacteremia was seen in 1 subject in the Enbrel 25 mg arm, 2 in the Enbrel 10 mg arm and none in the MTX arm.

The second most common SAE in the trial was malignancy. Six malignancies were diagnosed during the 12 months of observation during the trial. Three occurred in the Enbrel 25 mg arm: one case of prostate ca, one lung carcinoid and one Hodgkin's disease. Two occurred in the Enbrel 10 mg arm: one case of breast ca and one of lung ca. One case occurred in the MTX arm: a case of colon ca. In addition, at the beginning of the second year on study drug, one additional case was diagnosed: a case of bladder ca in the methotrexate arm.

The third most common SAE occurring during the trial was the category of thromboembolic events. No thromboembolic events were observed in the methotrexate arm, while two cases each were seen in the two Enbrel arms. In the Enbrel 25 mg arm, there were two cases of deep vein thrombosis. One case occurred after 3 months on study drug in a patient receiving oral contraceptive pills. The other occurred following one week on study drug in a patient with a Baker's cyst. In the Enbrel 10 mg arm, there was one case of deep vein thrombosis occurring 2 weeks on study drug in a subject with no known risk factors. The other case was a massive pulmonary embolus associated with a diagnosis of lung cancer.

Table 5. SAEs occurring in trial 16.0012

	MTX	10 mg	25 mg
Infections	4	4	5
Malignancy (excl. skin)	1	2	3
DVT, pulm. Embolus	0	2	2
Interstitial pneumonitis	3	0	0
Angina, MI	4	3	0
Other	9	3	8
Total cases (patients):	21 (17)	14 (9)	18 (15)

Table 6. Infectious SAEs occurring in trial 16.0012

MTX	Enbrel 10	Enbrel 25
Pneumonia (3)	Pneumonia	Pneumonia (3)
UTI	Bacteremia (2)	Sepsis
	Septic arthritis	

D. Discontinuations due to toxicity

As noted above, a higher proportion of subjects in the Enbrel 25 mg arm completed 12 months of dosing with assigned study drug than in the methotrexate arm. A total of 21 subjects discontinued study drug in the methotrexate arm compared to 10 in the Enbrel 25 mg arm and 9 in the Enbrel 10 mg arm ($p = 0.016$, MTX vs. all Enbrel). The reasons for discontinuation due to adverse events are given in table 7. The most common adverse events leading to discontinuation were alopecia, oral/nasal ulcers and vomiting, adverse events associated with methotrexate use. These events occurred in 9 subjects in the methotrexate arm and none in the Enbrel arms. Infection led to discontinuation in 3 subjects in the methotrexate arm and 3 and 1 in the Enbrel 10 mg and 25 mg arms, respectively. A diagnosis of a malignancy led to discontinuation in 1 subject in the methotrexate arm and two each in the Enbrel arms. MTX pneumonitis was observed in 3 subjects in the methotrexate and none in the Enbrel arms. Finally, injection site reaction (ISR) led to discontinuation in one subject in the Enbrel 25 mg arm. Other adverse events leading to discontinuation were evenly distributed in the 3 arms of the trial.

Table 7. Adverse events leading to discontinuation of study drug

	MTX	Enbrel 10	Enbrel 25
Alopecia, oral/nasal ulcers, vomiting	9	0	0
Infection	3	3	1
Malignancy	1	2	2
MTX pneumonitis	3	0	0
ISR	0	0	1
Other AEs	5	4	6

E. Other adverse events

Adverse events were reported by a higher proportion of subjects in the methotrexate arm than the two Enbrel arms: 95% vs. 90% and 89% in the Enbrel 10 mg and 25 mg arms respectively ($p = 0.010$, methotrexate vs combined Enbrel arms). The ten most common adverse events were headache, nausea, rash, rhinitis, diarrhea, bleeding at injection site, asthenia, dyspepsia, abdominal pain and dizziness. Of these, the only adverse event occurring at least 2% more commonly in the Enbrel 25 mg arm than the methotrexate arm was bleeding at injection site (14% vs. 10%).

G. Laboratory toxicities

One laboratory abnormality, low absolute neutrophil count (ANC), was seen more frequently in the subjects receiving Enbrel than subjects in the methotrexate arm: 16% of subjects in the Enbrel 25 mg arm vs. 8% in the methotrexate arm. The majority of these cases were grade 1 or 2. Grade 3 cases (ANC of 500-1000 cells/mm^3) of low ANC were seen in 3 subjects in the Enbrel 25 mg arm and 2 in the methotrexate arm. No grade 4 cases were observed. Laboratory abnormalities observed at a higher frequency in the methotrexate arm than the Enbrel arms of the trial are shown in table 8.

Table 8. Abnormal laboratory values

	MTX	Enbrel 10	Enbrel 25
Higher in Enbrel:			
Low ANC	18 (8%)	21 (10%)	34 (16%)
Higher in MTX:			
Hi SGOT	70 (32%)	31 (15%)	34 (16%)
Hi SGPT	96 (44%)	47 (23%)	49 (24%)
Lo lymphs	172 (79%)	142 (68%)	115 (56%)
Lo albumin	104 (48%)	89 (43%)	88 (43%)
Lo Hb	83 (38%)	79 (38%)	53 (26%)

H. Long-term safety studies

In previous controlled trials of Enbrel in rheumatoid arthritis, two adverse events were observed more frequently in subjects treated with Enbrel than those treated with placebo: injection site reactions and infections. The major contributor to the higher rate of infection was upper respiratory tract infection in the controlled portions of the trials, but in the long-term open-label studies, there were cases were observed of patients with serious infections. The significance of these serious infections was difficult to assess because of the lack of a control arm for the open-label trials. At the time of licensure of Enbrel in November, 1998, Immunex agreed to carry out a long-term safety study (16.0018) to assess the safety of long-term treatment with Enbrel. The study was designed as a 3-year, open-label study of 1200 subjects receiving Enbrel, measuring the rate of overall mortality, and the incidence of serious infection, malignancy and autoimmune disease. These rates were to be compared to historical control databases.

At present, there are 782 subjects included in the database. A total of 71 patients have been followed for 2-3 years and 502 for 1-2 years. Of the adverse events observed in this study, none occurred with an incidence higher than in controlled trials, and none of the adverse events has occurred with an incidence increasing with longer duration of exposure to Enbrel.

Overall, the types of infection seen with long-term exposure to Enbrel are similar to those seen in the controlled trials. No infection has been observed with an incidence increasing with longer duration of exposure to Enbrel. Serious infections were defined as those associated with hospitalization or intravenous antibiotics. Serious infections have been

observed at a rate of 5.5/100 patient-years. The serious infections are those expected for patients with rheumatoid arthritis in the age group under study. No increase in the rate of serious infection has been observed with longer duration of exposure to Enbrel.

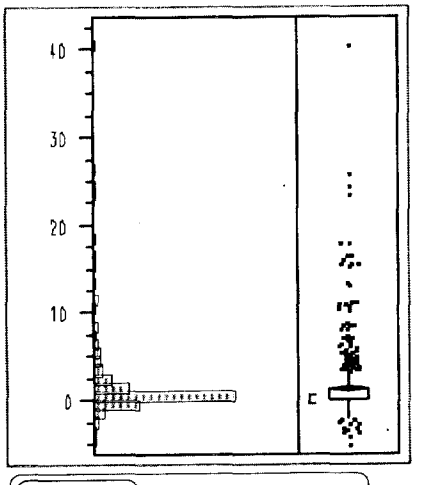
SUMMARY:

Although certain questions exist about assumptions used to assess the efficacy of Enbrel in delaying structural damage in study 16.0012, other data not using these assumptions support the safety and efficacy of Enbrel in this area. Data from the controlled trial do not suggest significant safety concerns. A large study currently underway, however, addresses concerns that Enbrel may have adverse effects in particular subpopulations.

VII. Appendices

Appendix 1. Skewed distribution of data for radiographic progression

Shown below is the distribution of estimated annual progression in total Sharp score for all subjects in the trial. On the y-axis is the annual progression rate. The left portion of the figure is a histogram with the distribution of values. The right portion of the figure is a box plot showing the median value, the upper and lower quartiles and the 10^{th} and 90^{th} percentiles. Outliers are shown as dots.



Quantiles		
maximum	100.0%	40.658
	99.5%	24.543
	97.5%	13.372
	90.0%	[illegible]
quartile	75.0%	1.406
median	50.0%	0.221
quartile	25.0%	0.039
	10.0%	-0.443
	2.5%	-1.862
	0.5%	-3.515
minimum	0.0%	-4.931