CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103795 / S- 5109

Trade Name: **Enbrel**

Generic Name: **etanercept**

Sponsor: **Immunex Corporation**

Approval Date: **June 5, 2003**

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APPROVAL LETTER

Product Approval Information - Licensing Action

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

June 5, 2003

Our STN: BL 103795 / 5109

Douglas Hunt
Immunex Corporation
One Amgen Center Drive
Mailstop 24-2-C
Thousand Oaks , CA 91320

Dear Mr. Hunt:

Your request to supplement your biologics license application for Etanercept to revise the package insert to include information regarding concurrent Etanercept and Anakinra therapy has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

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

Sincerely yours,

--- signature ---

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

Center for Biologics Evaluation and Research

Last Updated: 6/17/2003

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Date created: September 25, 2003

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LABELING

ENBREL®
(etanercept)

Prescribing Information

DESCRIPTION

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

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

CLINICAL PHARMACOLOGY

General

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

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms.[5] Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.[6, 7] Etanercept inhibits

binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive.[7] Cells expressing transmembrane TNF that bind ENBREL® are not lysed in vitro in the presence or absence of complement.[7]

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).[7]

Pharmacokinetics

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

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

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

CLINICAL STUDIES

Adult Rheumatoid Arthritis

The safety and efficacy of ENBREL® were assessed in three randomized, double-blind, controlled studies. Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g., hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL® or placebo were administered SC twice a week for 6 consecutive months. Results from patients receiving 25 mg are presented in Table 1.

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

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

The results of all three trials were expressed in percentage of patients with improvement in RA using American College of Rheumatology (ACR) response criteria.[8]

Clinical Response

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

Table 1
ACR Responses in Placebo- and Active-Controlled Trials

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

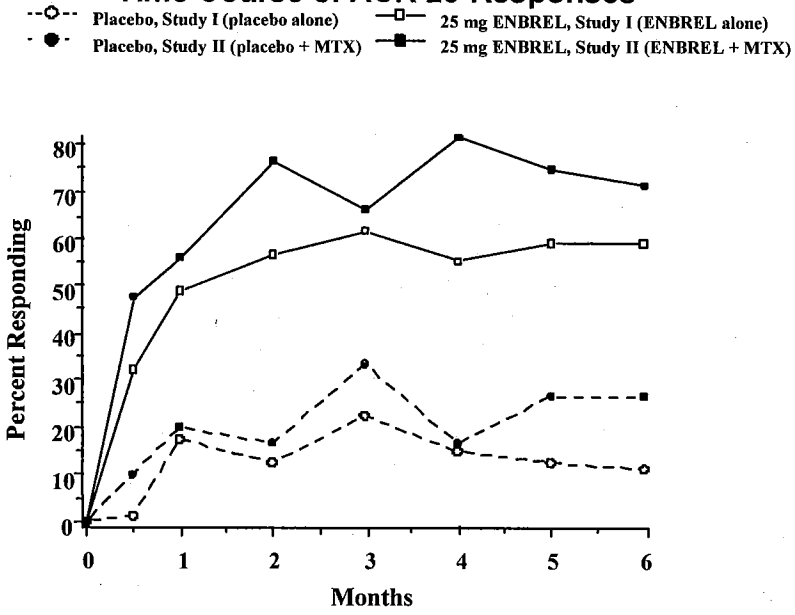
[a] 25 mg ENBREL® SC twice weekly.

[b] $p < 0.01$, ENBREL® vs. placebo.

[c] $p < 0.05$, ENBREL® vs. MTX.

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

Figure 1
Time Course of ACR 20 Responses



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

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

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

Table 2
Components of ACR Response in Study I

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

* Results at 6 months showed similar improvement.

a 25 mg ENBREL® SC twice weekly.

b Scale 0-71.

c Scale 0-68.

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

e Health Assessment Questionnaire[9]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

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

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

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

A Health Assessment Questionnaire (HAQ),[9] which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during Studies I and III. All subdomains of the HAQ were improved in patients treated with ENBREL®.

In Study III, health outcome measures were assessed by the SF-36 questionnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).[10] At 12 months, patients treated with 25 mg ENBREL® showed significantly more improvement in the PCS compared to the 10

mg ENBREL® group, but not in the MCS. Improvement in the PCS was maintained over the 24 months of ENBREL® therapy.

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

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 3. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

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

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

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

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

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

Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)

The safety and efficacy of ENBREL® were assessed in a two-part study in 69 children with polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 years with moderately to severely active polyarticular-course JRA refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) ENBREL® SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on ENBREL® or receive placebo for four months and assessed for disease flare. Responses were measured using the JRA Definition of Improvement (DOI),[11] defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a ≥ 30% worsening in three of the six JRA core set criteria and ≥ 30% improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.[12] In part 2, 6 of 25 (24%) patients remaining on ENBREL® experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received ENBREL® and 28 days for patients who received placebo. Each component of the JRA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on ENBREL®. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on ENBREL® continued to improve from month 3 through month 7, while those who received placebo did not improve.

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

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

Psoriatic Arthritis

The safety and efficacy of ENBREL® were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement (n = 104); (2) polyarticular

arthritis (absence of rheumatoid nodules and presence of psoriasis; n = 173); (3) arthritis mutilans (n = 3); (4) asymmetric psoriatic arthritis (n = 81); or (5) ankylosing spondylitis-like (n = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients currently on MTX therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg ENBREL® or placebo were administered SC twice a week for 6 months.

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

Table 4

Components of Disease Activity in Psoriatic Arthritis

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

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

[b] Scale 0-78.

[c] Scale 0-76.

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

[e] Health Assessment Questionnaire[9]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f] Normal range: 0 – 0.79 mg/dL

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

The skin lesions of psoriasis were also improved with ENBREL®, relative to placebo, as measured by percentages of patients achieving improvements in the psoriasis area and severity

index (PASI).[14] Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the ENBREL® group (n = 66), compared to 18% and 3%, respectively, in the placebo group (n = 62). Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline.

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

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

WARNINGS

INFECTIONS

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

OF ENBREL® IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see PRECAUTIONS and ADVERSE REACTIONS, Infections).

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

Neurologic Events

Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL® therapy. The causal relationship to ENBREL® therapy remains unclear. While no clinical trials have been performed evaluating ENBREL® therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.[15, 16] Prescribers should exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

Hematologic Events

Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ENBREL®. The causal relationship to ENBREL® therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL® who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL®. Discontinuation of ENBREL® therapy should be considered in patients with confirmed significant hematologic abnormalities.

Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 109/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

PRECAUTIONS

General

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

Information to Patients

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

Immunosuppression

Anti-TNF therapies, including ENBREL®, affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL®, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL® on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections,** and **Malignancies**). The safety and efficacy of ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

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

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

Autoimmunity

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

Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy (Category B)

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

Nursing Mothers

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

Geriatric Use

A total of 197 RA patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

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

ADVERSE REACTIONS

Adverse Reactions in Adult Patients with RA or Psoriatic Arthritis

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

Injection Site Reactions

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

Infections

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

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

In all clinical trials in RA, serious infections experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in ENBREL®- and placebo-treated patients from controlled trials. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL®. Some have occurred within a few weeks after initiating treatment with ENBREL®. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL® treatment may increase mortality in patients with established sepsis.[17]

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

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving ENBREL® alone or in combination with immunosuppressive agents.

Malignancies

Patients have been observed in clinical trials with ENBREL® for over 3 years. The incidence of malignancies has not increased with extended exposure to ENBREL® and is similar to that expected when projected from the National Cancer Institute's Surveillance, Epidemiology and End Results database.[18]

Immunogenicity

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

The data reflect the percentage of patients whose test results were considered positive for antibodies to ENBREL® in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to ENBREL® with the incidence of antibodies to other products may be misleading.

Autoantibodies

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

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

Other Adverse Reactions

Table 5 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL® compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III. Adverse events in the psoriatic arthritis trial were similar to those reported in RA clinical trials.

Table 5
Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

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

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

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

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

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

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

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

Adverse Reactions in Patients with JRA

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

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

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

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

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

Adverse Reaction Information from Spontaneous Reports

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

Additional adverse events are listed by body system below:

Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular:	chest pain, vasodilation (flushing)
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)
Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
Nervous:	paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see **WARNINGS**)
Ocular:	dry eyes, ocular inflammation
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

OVERDOSAGE

The maximum tolerated dose of ENBREL® has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during

clinical trials of ENBREL®. Single IV doses up to 60 mg/m^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

DOSAGE AND ADMINISTRATION

Adult RA and Psoriatic Arthritis Patients

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

JRA Patients

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

Preparation of ENBREL®

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

Note: The needle cover of the diluent syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.

ENBREL® should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL®. During reconstitution of ENBREL®, the diluent should be injected very slowly into the vial. Some foaming will occur. This is normal. To avoid excessive foaming, **do not shake or vigorously agitate**. The contents should be swirled gently during dissolution. Generally, dissolution of ENBREL® takes less than 10 minutes. Reconstitution with the supplied BWFI yields a multiple-use, preservative solution that expires 14 days after reconstitution. For pediatric patients to be treated with less than a 25 mg dose, write the date in the area marked "Mixing Date:" on the supplied sticker and attach the sticker to the vial immediately after reconstitution. Contents of one vial of ENBREL® solution should not be mixed with, or transferred into the contents of another vial of ENBREL®. No other medications should be

added to solutions containing ENBREL®, and do not reconstitute ENBREL® with other diluents. Do not filter reconstituted solution during preparation or administration.

Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains.

Administration of ENBREL®

Withdraw the solution into a syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial.

Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. See **How to Use ENBREL®, Instructions for Preparing and Giving an Injection** instruction sheet for detailed information on injection site selection and dose administration.

Storage and Stability

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

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

HOW SUPPLIED

ENBREL® is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one syringe containing 1 mL Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol), one plunger, and two alcohol swabs.

Rx only

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AMGEN®

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103795 / S- 5109

MEDICAL REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

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

September 12, 2003

From: Li-ching Liang, M.D.

Through: Jeffrey Siegel, M.D. Acting Chief, Immunology and Infectious Disease Branch

Marc Walton, M. D. Acting Assistant Director, Division of Clinical Trials Design and Analysis, Office of Therapeutics Research and Review, CBER, FDA

To: STN 103795/5109

Topic: Clinical Review

Biologic License Application: STN 103795/5109
Product: Etanercept
Indication: Combination Etanercept and Anakinra Therapy
Sponsor: Immunex Corporation

CC: Karen Weiss, M.D.,
Office Director
CDER/OTRR/DCTDA

Review of BLA supplement STN 103795/5109/000

Sponsor:	Immunex Corporation, CA, USA
Product:	Etanercept, soluble dimeric fusion protein to TNF-α
Submission Date:	November 8, 2002
Review Date:	May 20, 2002
Clinical Reviewer:	Li-ching Liang, MD, FACP, FACG
Material Reviewed:	Electronic submission consisting of: a cover letter, a form 356, complete study reports on 2 clinical trials #20000125 and #20000223 in rheumatoid arthritis patients.

Changes in the package insert proposed by the sponsor in this sBLA:

- Label changes to include in the bolded **WARNINGS** section the statement: **"In a 24-week study of concurrent Enbrel ® and anakinra therapy, the rate of serious infections in the combination arm (7%) was higher than with Enbrel® alone (0%). The combination of Enbrel® and anakinra did not result in higher ACR response rates compared to Enbrel® alone (See Clinical Studies, Clinical Response)."**

- To change the threshold definition for neutropenia from [redacted] < 1 x 10^9.

- To include in the Drug Interactions section under PRECAUTIONS the statement: **"Specific drug interaction studies have not been conducted with Enbrel®. However, in a study in which patients with active RA were treated for up to 24 weeks with concurrent Enbrel® and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with Enbrel® alone (0%). Two percent of patients treated concurrently with Enbrel ® and anakinra developed neutropenia (ANC < 1 x 10^9/L)."**

- To include in the Hematologic Events section under ADVERSE REACTIONS the statement: **"Two percent of patients treated concurrently with Enbrel ® and anakinra developed neutropenia (ANC < 1 x 10^9/L). While neutropenic, one patient developed cellulitis which recovered wih antibiotic therapy."**

TABLE OF CONTENTS

I. INTRODUCTION

Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are important mediators in the pathogenesis of rheumatoid arthritis (RA). TNF-α stimulates bone and cartilage resorption, inhibits bone formation and proteoglycan synthesis in vitro, and facilitates inflammatory cell infiltration by stimulating adhesion of neutrophils to endothelial cells. Elevated levels of TNF are found in the synovial fluid of RA patients and in both the synovium and psoriatic plaques of patients with psoriatic arthritis. Two distinct receptors for TNF (TNFRs) exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biologic activity of TNF is dependent upon binding to either cell surface TNFR. In animal arthritis studies, TNF-α appears to be synergistic with IL-1 in the inflammatory process.

The appearance of IL-1 in synovial fluid from patients with RA seems to correlate with acute inflammation of the joints, and production of IL-1 in vitro by synovial tissues from subjects with RA has been correlated with arthroscopic results, indicating the extent of inflammation. IL-1 also stimulates synoviocytes to product prostaglandins and metalloproteinases which are responsible for joint destruction. IL-1 receptor antagonist (IL-1Ra) is a naturally occurring protein that has been shown to effectively inhibit biologic responses elicited by IL-1 in vitro and in vivo.

A recombinant form of Il-1Ra, anakinra, was recently approved in the US for the treatment of RA. Several large, placebo-controlled trials have evaluated the efficacy and safety of anakinra, both alone and in combination with methotrexate (MTX), in relieving the signs and symptoms of RA, and an ongoing study evaluates the ability of anakinra to retard the underlying structural damage to bone and cartilage. Anakinra has received marketing approval in the US, Europe, and Canada for the treatment of the signs and symptoms of RA.

One therapy that targets TNF-α is etanercept, an approved , soluble TNF-α receptor. In clinical practice, rheumatologists may be interested in the possibility of prescribing anakinra in combination with other therapies such as etanercept for RA that target pro-inflammatory cytokines. Two RA studies combining etanercept with anakinra (#20000125 and #20000223) are discussed in this review.

II. Protocol 20000125

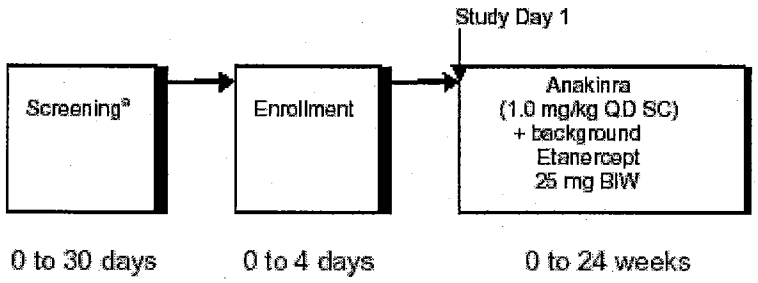
A Multicenter Open-label Study to Evaluate the Safety of Daily Subcutaneous Injections of Anakinra (r-metHuIL-1ra) in Subjects with Rheumatoid Arthritis Using Etanercept.

The primary objective of this study was to evaluate the safety of anakinra in subjects with RA using background etanercept, a soluble TNF-α receptor. The secondary objective was to observe disease progression in subjects with RA using anakinra and background etanercept.

A. Study Design

Protocol #20000125 was an open-label, multicentered, Phase 2, 24-week, single-arm study conducted at 9 U.S. sites (from June 20, 2000 to April 2, 2001) in which all subjects received subcutaneous (SC) injections of anakinra 1.0 mg/kg/day for 24 weeks while already on background etanercept 25 mg twice weekly (BIW) for at least 12 weeks. The study design is shown in **Figure 1** below:

Figure 1: Study #20000125 Design Schema



[a] Includes 4 week DMARD washout period as necessary.

The study was designed to be implemented rapidly and provide an overview of potentially significant safety concerns that might be associated with combination anakinra/etanercept therapy. As a result, the study did not have a control arm. Subsequent studies were planned to include active control groups allowing a comparison of the safety profile of combined therapy with the profile for 1 or both therapies alone.

This study was conducted at 9 US sites and enrolled 58 patients who had a mean age of 49 yrs, were predominantly women (85%), and White (86%). The inclusion criteria were:

- A diagnosis of RA as determined by ACR criteria.
- Active RA as defined by a minimum of 6 tender and 6 swollen joints (excluding the distal interphalanges).
- Subject must have been receiving 25 mg etanercept BIW for at least 12 weeks before enrollment. All other DMARDs were prohibited.
- Age >18 years at the time of diagnosis of RA.
- Doses of corticosteroids (≤ 10mg/day of prednisone or equivalent) must have been kept stable for at least 4 weeks before enrollment.

No other investigational agents were allowed during the study (from screening visit through study week 24). In addition, the following medications were proscribed: live vaccines, azathioprine, cyclophosphamide, cyclosporine, gold, hydroxychloroquine, infliximab, leflunomide, methotrexate, mycophenolate mofetil, prosorba column, sirolimus, sulfasalazine, and tacrolimus. The 1.0 mg/kg/day anakinra dose was chosen because it was within the range of doses found to be consistently efficacious as a single agent in previous clinical trials. The 25mg BIW dose of etanercept was chosen because it is the approved dose of etanercept. All subjects received the same open-label treatment with anakinra 1.0 mg/kg/SC QD against a background of SC etanercept 25 mg BIW. Analysis was descriptive with no interim analysis performed. Missing data were not imputed and joints that received an intra-articular corticosteroid injection were considered "failed" joints.

Adverse events and measures of disease activity were assessed at every study visit. Clinical laboratory measures were assessed at all visits other than week 2. Baseline subject demographics are summarized in **Table 1** and baseline disease measures are summarized in **Table 2.**

B. Endpoints

The primary safety endpoint in this study was the subject incidence of serious adverse events (SAEs). Disease activity endpoints were: 1) number of tender and painful joints, 2) number of swollen joints, 3) HAQ, and 4) ESR and CRP. Subjects receiving at least 1 dose of anakinra were considered evaluable for the safety analyses and the summary of disease progression.

C. Study Population

Patients in this study were predominantly female (85%) and white (86%), (**Table 1**) with the majority of patients (83%) on NSAIDs with over half the patients (53%) on corticosteroids (**Table 2**). The mean age of patients in this study was 49 years, with a 12 year mean duration of rheumatoid arthritis. Patients had a mean tender joint count of 26 and a swollen joint count of 17, indicative of moderately active disease .

Table 1: Summary of Baseline Demographics

	Anakinra and Etanercept N = 58	
Gender - n (%)		
Male	9	(16)
Female	49	(85)
Ethnic group - n (%)		
White or Caucasian	50	(86)
Black or African American	1	(2)
Hispanic or Latin	4	(7)
Asian	2	(3)
Japanese	0	(0)
American Indian or Alaska Native	1	(2)
Native Hawaiian or Other Pacific Islander	0	(0)
Aborigine	0	(0)
Other	0	(0)
Age (yr)		
Mean	48.9	
Weight (kg)		
Mean	81.12	

Table 2: Summary of Baseline Characteristics

	Anakinra and Etanercept N = 58	
NSAIDs use- n (%)		
No	10	(17)
Yes	48	(83)
Corticosteroid use - n (%)		
No	27	(47)
Yes	31	(53)
Duration on Etanercept before baseline (yr)		
Mean	1.2	
Duration of rheumatoid arthritis (yr)		
Mean	11.9	
C-reactive protein (mg/dL)		
Mean	2.19	
ESR (mm/hr)		
Mean	25.1	
Tender/painful joints (0-68)		
Mean	26.4	
Swollen joints (0-66)		
Mean	17.4	
Health assessment questionaire (0-3)		
Mean	1.2	

N = Number of subjects who were enrolled
[a] Values below detection limit are set to 0.09 for C-reactive protein

D. Study Conduct and Subject Disposition

A total of 58 subjects entered this study (**Table 3**); 37 (64%) completed the study and 21 (36%) withdrew prematurely. Most of the premature withdrawals were the result of either adverse events (11 subjects, 19%) or withdrawal of consent (8 subjects, 14%). Eight subjects were known to have significant protocol deviations during the study; all were violations of eligibility criteria and were randomly distributed across study sites. None were likely to have impacted on the outcome of the study and none resulted in any changes to the analysis of the study results. 87% of subjects who completed the study were at least 90% compliant with the treatment regimen. The rate of missed injections across all 58 subjects entered in the trial (number of missed injections/number of expected injections) was 3.5%. Subjects had RA at baseline for a mean of 12 years and had used etanercept for the treatment of RA for a mean of 1.2 years.

Table 3: Summary of Subject Disposition

	Anakinra and Etanercept N = 58	
	n	(%)
Total enrolled	58	(100)
Never received study drug	0	(0)
Completed study	37	(64)
Withdrew prematurely	21	(36)
Reason for premature withdrawal		
Ineligibility determined	0	(0)
Protocol deviation	0	(0)
Adverse event	11	(19)
Consent Withdrawn	8	(14)
Administrative Decision	1	(2)
Lost to follow-up	0	(0)
Death	0	(0)
Other	1	(2)

E. Efficacy Evaluation

Changes from baseline TJC (**Table 4**), SJC (**Table 5**) , and HAQ scores (**Table 6**) showed improvements of 34%, 41%, and 25%, respectively at week 24. At the study's end at week 24, mean TJC improvement was 9.1, mean SJC improvement was 7.1, and mean HAQ score improvement was 0.3. Both mean CRP and ESR (**Table 7** and **Table 8**) values showed modest decreases from baseline at every visit though there was variability at the different study visits. Overall, the results suggested improvement from baseline in all measures throughout the study, but because of the open-label nature of the study, the results should be interpreted with caution. In addition, the degree of improvement may have been exaggerated if patients doing less well selectively dropped out of the study.

Changes in CRP were variable in this study as indicated by both the fluctuating mean weekly changes from baseline values. While the mean values at every study visit indicated improvement compared to baseline, no pattern of progressive improvement was evident coinciding with the administration of anakinra to etanercept. Likewise, changes in ESR levels at each visit were decreased compared to baseline, but mean values fluctuated and did not demonstrate a consistent reduction over time.

Table 4: Change from Baseline of Tender/Painful Joint Count

Treatment	Anakinra and Etanercept N = 58
Week 2	
Mean	-3.9
Week 4	
Mean	-6.4
Week 8	
Mean	-8.1
Week 12	
Mean	-6.5
Week 24	
Mean	-9.1

Table 5: Change from Baseline of Swollen Joint Count

Treatment	Anakinra and Etanercept N = 58
Week 2	
Mean	-2.8
Week 4	
Mean	-4.5
Week 8	
Mean	-5.9
Week 12	
Mean	-6.2
Week 24	
Mean	-7.1

Table 6: Change from Baseline of Health Assessment Questionnaire

Treatment	Anakinra and Etanercept N = 58
Week 2	
Mean	-0.1
Week 4	
Mean	-0.2
Week 8	
Mean	-0.2
Week 12	
Mean	-0.2
Week 24	
Mean	-0.3

Table 7: Change from Baseline of C-reactive Protein (mg/dL)

Treatment	Anakinra and Etanercept N = 58
Week 2	
Mean	-0.9
Week 4	
Mean	-0.6
Week 8	
Mean	-0.3
Week 12	
Mean	-1.3
Week 24	
Mean	-0.7

Table 8: Change from Baseline of Erythrocyte Sedimentation Rate (mm/hr)

Treatment	Anakinra and Etanercept N = 58
Week 2	
Mean	-4.1
Week 4	
Mean	-5.9
Week 8	
Mean	-5.3
Week 12	
Mean	-10.4
Week 24	
Mean	-5.7

F. Safety Evaluation

1. Subject Exposure

The mean exposure to anakinra during this study was 0.35 years, (**Table 9**). On average, subjects missed fewer than 4% of their scheduled anakinra injections.

Table 9: Summary of Subject Exposure to Study Drug

	Anakinra and Etanercept N = 58
Subject years of exposure to study drug	
n	58
Mean	0.346
SD	0.170
Median	0.457
Minimum	0.016
Maximum	0.517
Number of missed injections / Number of expected injections	
n	58
Mean	0.035
SD	0.065
Median	0.000
Minimum	0.000
Maximum	0.306

2. Deaths and Malignancies

No subjects died and no malignancies were reported during participation in this study.

3. Serious Adverse Events

Serious adverse events were reported by 7 of 58 subjects (12%) who reported a total of eight SAEs in **Table 10.** The only serious events occurring in more than 1 subject were pneumonia and cellulitis, in 2 subjects each.

Table 10: Crude and Exposure-adjusted Subject Incidence of Treatment-emergent Adverse Events: Serious Adverse Events.

Treatment group	Anakinra and Etanercept N = 58		
Number of subjects reporting AEs	7	12%	0.359
BODY SYSTEM Preferred Term	n	Crude	Exp. Adj.
BODY AS A WHOLE	2	(3.4)	0.102
Injury	1	(1.7)	0.051
Withdrawal Syndrome	1	(1.7)	0.050
GASTROINTESTINAL	2	(3.4)	0.100
Abscess Abdomen	1	(1.7)	0.050
Gastric Ulcer Hemorrhagic	1	(1.7)	0.050
RESPIRATORY	2	(3.4)	0.100
Pneumonia	2	(3.4)	0.100
SKIN AND APPENDAGES	2	(3.4)	0.100
Cellulitis	2	(3.4)	0.100

N = Number of subjects who received at least 1 dose of study drug
n = Number of subjects reporting at least 1 occurrence of an adverse event
Crude = n / N. The 95% confidence intervals for 0 crude rate: All = (0.0, 6.2)
Exp. Adj. = Subject incidence per subject year of exposure. Subject year of exposure is the duration between the date of first dose of study drug and the date of last dose of study drug, data cutoff date or date of first occurrence of the event in the study period, whichever comes first.

a) SAE Narratives

Details of the 7 subjects with eight SAEs are provided in the following narratives:

Subject 1 (#202): This was a 57 y.o. woman with RA who developed **cellulitis at the abdominal wall** injection site 6 weeks after beginning anakinra. Patient was treated with IV antibiotics and study medication was discontinued. She subsequently developed an **abdominal wall abscess** at the site of the cellulitis which was treated by incision and drainage. Patient was eventually withdrawn from the study.

Subject 2 (#506): This was a 56 y.o. man with RA on anakinra x 5.5 months, who developed **facial cellulitis** after 5 months of anakinra treatment. He was given IV and oral antibiotics and completed the study.

Subject 3 (#603): This 29 y.o. woman developed **pneumonia** and **pleurisy** after 4 months on anakinra and withdrew from the study. Patient was hospitalized, and given IV antibiotics followed by oral antibiotics.

Subject 4 (#901): This 66 y.o. woman developed **pneumonia** after 3 months of anakinra. She was placed on antibiotics, recovered from the incident after 49 days, and withdrawn from the study.

Subject 5 (#306): This was a 47 y.o. woman with RA and a history of NSAID use who was hospitalized with a **bleeding gastric ulcer** after 5 months of anakinra use. Study medication was interrupted but restarted; patient completed the study.

Subject 6 (#804): This 45 y.o. woman with RA experienced fatigue and influenza-like symptoms after 4 months of anakinra use. She sustained a fall complicated by a laceration, severe left jaw pain, and a suspected fracture. She also developed a tonic-clonic seizure with blood levels of sertraline, butalbital, caffeine, theophylline, and phenytoin. Patient was diagnosed with **withdrawal syndrome** from a combination of opiates and barbiturates. She was discontinued from the study due to personal problems.

Subject 7 (#809): This 40 y.o. woman was **electrocuted** after touching faulty electrical wiring at home. She was hospitalized for observation of cardiac irregularities and burn treatment. The patient completed the study.

b) Serious Infections

Serious infections were reported in 4 subjects (7%) during this study (**Table 11**). These serious infections included 2 subjects with pneumonia, 1 with cellulitis, and 1 with cellulitis leading to abdominal wall abscess. Serious infections were considered possibly related to study medication and resulted in withdrawal from the study in 3 of 4 subjects. No unusual, opportunistic infections, or tuberculosis were reported during this study.

Table 11. Crude and Exposure-adjusted Subject Incidence of Treatment-emergent Adverse Events: Serious Infectious Episodes

Treatment group	Anakinra and Etanercept N = 58		
Number of subjects reporting AEs	4	6.9%	0.199
BODY SYSTEM Preferred Term	n	Crude	Exp. Adj.
RESPIRATORY	2	(3.4)	0.100
Pneumonia	2	(3.4)	0.100
SKIN AND APPENDAGES	2	(3.4)	0.100
Cellulitis	2	(3.4)	0.100
GASTROINTESTINAL	1	(1.7)	0.050
Abscess Abdomen	1	(1.7)	0.050

N = Number of subjects who received at least 1 dose of study drug
n = Number of subjects reporting at least 1 occurrence of an adverse event
Crude = n / N. The 95% confidence intervals for 0 crude rate: All = (0.0, 6.2)
Exp. Adj. = Subject incidence per subject year of exposure. Subject year of exposure is the duration between the date of first dose of study drug and the date of last dose of study drug, data cutoff date or date of first occurrence of the event in the study period, whichever comes first.

4. Adverse Events

Table 12 provides an overview of the adverse events observed during the study. 93% of subjects had at least one adverse event. 7 patients (12%) had SAEs and 83% had application site events. 28 (48%) of patients had infectious episodes, of which 4 (7%) were considered serious (see above). Infections reported by more than 3 subjects were upper respiratory infections (URI) in 13 subjects (22%), and influenza-like symptoms and urinary tract infection (UTI), reported by 4 subjects each (7%). Eleven subjects (19%) withdrew from the study because of adverse events. The only preferred term associated with withdrawal in more than a single subject was pneumonia, in 2 subjects. The body system with the most withdrawal events was the Respiratory System with 3 subjects.

Table 12: Overall Summary of Adverse Events

	Anakinra and Etanercept (N = 58) n	(%)
Subjects with any adverse event	54	(93)
Severe events	7	(12)
Serious adverse events	7	(12)
Application site events	48	(83)
Infectious episodes	28	(48)
Serious infectious episodes	4	(7)
Discontinuations due to Adverse events	11	(19)
Deaths on study	0	(0)

The most common AE in this study by body system was irritation at the injection site, reported by 83% of subjects. Other common adverse events by preferred term (**Table 13**) were URI (31%), worsening of RA (16%), headache (12%), sore throat (9%), and influenza-like symptoms (9%).

Table 13: Crude and Exposure-adjusted Subject Incidence of Treatment-emergent Adverse Events: Events Occurring in ≥ 5% of Subjects

Treatment group	Anakinra and Etanercept N = 58		
Number of subjects reporting AEs	54	93%	27.167
BODY SYSTEM Preferred Term	n	Crude	Exp. Adj.
APPLICATION SITE	48	(83%)	11.146
Injection Site Erythema	31	(53%)	3.201
Injection Site Pruritus	24	(41%)	2.106
Injection Site Pain	16	(28%)	1.062
Injection Site Rash	9	(16%)	0.515
Injection Site Inflammation	6	(10%)	0.326
Injection Site Urticaria	4	(7%)	0.219
Injection Site Ecchymosis	3	(5%)	0.161
RESPIRATORY	31	(53%)	2.345
Infection Upper Respiratory	18	(31%)	1.106
Sore Throat	5	(9%)	0.260
Rhinitis	4	(7%)	0.210
Sinusitis	4	(7%)	0.208
Allergic Rhinitis	3	(5%)	0.157
Bronchitis	3	(5%)	0.158
Cough	3	(5%)	0.155
Upper Respiratory Tract Congestion	3	(5%)	0.153
MUSCULO-SKELETAL	20	(35%)	1.250
Arthritis Rheumatoid	9	(16%)	0.481
Pain Limb	3	(5%)	0.156
BODY AS A WHOLE	18	(31%)	1.210
Influenza-Like Symptoms	5	(9%)	0.256
Fatigue	4	(7%)	0.210
Edema Peripheral	3	(5%)	0.157
Fall	3	(5%)	0.155
GASTROINTESTINAL	15	(26%)	0.876
Constipation	3	(5%)	0.156
Diarrhea	3	(5%)	0.154
Nausea	3	(5%)	0.157
Vomiting	3	(5%)	0.152

Table 13 (cont'd): Crude and Exposure-adjusted Subject Incidence of Treatment-emergent Adverse Events: Events Occurring in ≥ 5% of Subjects

Treatment group	Anakinra and Etanercept N = 58		
Number of subjects reporting AEs	54	93%	27.167
BODY SYSTEM Preferred Term	n	Crude	Exp. Adj.
CNS/PNS	11	(19%)	0.655
Headache	7	(12%)	0.391
SKIN AND APPENDAGES	11	(19%)	0.636
REPRODUCTIVE (FEMALE)[a]	4	(8%)	0.254
PSYCHIATRIC DISORDER	4	(7%)	0.207
RESISTANCE MECHANISM	4	(7%)	0.211
URINARY DISORDERS	4	(7%)	0.208
Infection Urinary Tract	4	(7%)	0.208

N = Number of subjects who received at least 1 dose of study drug
n = Number of subjects reporting at least 1 occurrence of an adverse event
Crude = n / N. The 95% confidence intervals for 0 crude rate for overall / males / females: All = (0.0, 6.2) / (0.0, 29.9) / (0.0, 7.3)
Exp. Adj. = Subject incidence per subject year of exposure. Subject year of exposure is the duration between the date of first dose of study drug and the date of last dose of study drug, data cutoff date or date of first occurrence of the event in the study period, whichever comes first.
[a] Reproductive AE percents are based on the number of males / females evaluable for safety: All = 9 / 49

5. Clinical Laboratory Evaluation

Worsening in laboratory values that constituted an increase of ≥ 2 WHO grades occurred in 5 subjects (9%); all 5 were increases from grade 0 to grade 2. These included decreases in WBCs (1 subject), neutrophils (2 subjects), and lymphocytes (2 subjects). Using Immunex's proposed definition of neutropenia as "< 1.0×10^9/L" instead of [redacted], one of the two patients (**Table 14**) with neutropenia had a serious infection of cellulitis complicated by an abdominal wall abscess that appeared temporally related to neutropenia (lowest value was 0.68×10^9/L). The other patient with neutropenia had a lowest value of 1.47×10^9/L, which qualified as a Grade 2 adverse event according to the WHO toxicity criteria, but was higher than the 1.0×10^9 level discussed above.

Table 14: Neutrophils Shifts From Baseline in WHO Toxicity Grades

Treatment Group	Baseline Grade	Most Extreme On-Study Grade: Increase N/A	0	1	2	3	4	Decrease N/A	0	1	2	3	4
Anakinra and Etanercept (N = 58)	N/A							-	-	-	-	-	-
	0							2	43	8	2	-	-
	1			Not Applicable				-	-	2	-	-	-
	2							-	1	-	-	-	-
	3							-	-	-	-	-	-
	4							-	-	-	-	-	-

G. Discussion of Study 20000125 Results

This trial included no control group and subjects in the study had been receiving DMARDs including etanercept for widely varying periods before study entry. The study was not intended to provide precise characterization of the safety or efficacy of combination etanercept /anakinra treatment in RA; it was intended to provide rapid feedback on potentially clinically significant changes in the safety or disease status profiles relative to historical observations with either agent alone. **Table 15** below provides the rates of serious adverse events and other key safety measures seen in Study 20000125, their 95% confidence intervals, and corresponding incidence rates reported in the approved product labels for etanercept and anakinra.

Table 15: Percent of Subjects Experiencing Adverse Events in Anakinra and Etanercept Studies

	Study 20000125		Approved Product Labels [a]	
	Anakinra + Etanercept	95% CI	Anakinra	Etanercept [b]
Serious adverse events	12	5.0 - 23.3	--	4, 6
Infectious events	48	35.0 - 61.8	40	35, 64
Serious infections	7	1.9 - 16.7	1.8	1
URIs	31	19.5 - 44.5	13	29, 31
Application site events	83	70.6 - 91.4	71	34, 37

[a] Values given in the approved product labels for both products for 6-month Studies
[b] Where values from 2 different studies are available, both are given

While comparisons across studies must be undertaken with caution, the rate of serious infections observed with combination therapy (7%, 4 of 58 subjects) appeared to be higher in comparison with the results in studies of either agent alone. The lower limit of the 95% CI (1.9%) was above the incidence rate seen for either agent alone (1.8% for anakinra, 1% for etanercept). The nature of the serious infections, consisting of 2 cases each of pneumonia and cellulitis, was consistent with the safety profiles observed previously for both agents.

III. Protocol 20000223

A Multicenter Double-blind Study to Evaluate the Safety and Efficacy of Anakinra (r-metHuIL-1ra) and Etanercept in Subjects with Rheumatoid Arthritis using Methotrexate

The primary objective of protocol 20000223 was to evaluate the safety and efficacy of combined therapy with anakinra 100 mg QD and etanercept 25 mg BIW in subjects with RA using background MTX. The secondary objective was to evaluate the safety and efficacy of combined therapy with anakinra 100 mg SC QD and etanercept 25 mg QW in subjects with RA using background MTX.

This multicenter, double-blind, randomized, active-controlled study was designed to evaluate the safety and efficacy of 24 weeks of combination treatment with anakinra and etanercept in subjects with active RA who were receiving background MTX, but had not previously received treatment with any protein-based TNF-α inhibitor or anakinra.

The clinical hypothesis was that, for subjects with active RA despite MTX use, combination treatment with anakinra and etanercept would provide a superior clinical effect in improving signs and symptoms of RA as compared with etanercept alone. It was also hypothesized that combination treatment of anakinra and etanercept would be as safe as treatment with etanercept alone in these subjects.

A. Study Design

In this multicentered Phase II study, conducted March 26, 2001 to April 19, 2002, RA patients were randomized equally to 1 of 3 treatments:

- anakinra placebo QD + etanercept 25 mg BIW ("etanercept alone")
- anakinra 100 mg QD + etanercept 25 mg QW ("anakinra + etanercept QW")
- anakinra 100 mg QD + etanercept 25 mg BIW ("anakinra + etanercept BIW")

Treatments were administered by SC injection for 24 weeks. Subjects were blinded to the treatment group by administration of additional etanercept sham injections when necessary, so that all subjects received BIW injections of etanercept/sham and QD injections of anakinra or matched placebo. Subjects continued MTX treatment at the same stable dosage (in the range of 10 to 25 mg/week) and route of administration that they were receiving at baseline. Other medications taken regularly before entry into the study (eg, corticosteroids) were also continued at the same dose throughout the study.

After screening, subjects returned to the study center for study-related evaluations at baseline (day 1), and at weeks 2, 4, 8, 12, 16, 20, and 24. Subjects then had the option of enrolling in the open-label extension study, Amgen Protocol 20010190, in which they continued receiving anakinra treatment, and could have received etanercept at the investigator's discretion, for ≤ 12 weeks. For subjects who did not enroll in the extension study, a follow-up telephone evaluation was performed approximately 4 weeks after the week-24 visit or after early study discontinuation.

1. Primary Endpoint

The primary efficacy endpoint was the proportion of subjects with improvements of 50% in ACR response criteria at week 24. A positive ACR_{50} response was defined as at least a 50% improvement from baseline in both tender/painful and swollen joint counts, and a ≥ 50% improvement in ≥ 3 of the following 5 measures:

- Physician's global assessment of disease activity
- Subject's global assessment of disease activity
- Subject's assessment of pain
- Subject's functional status as measured by the Health Assessment Questionnaire (HAQ)
- Acute phase reactant (CRP or ESR)

2. Secondary Endpoints

Secondary efficacy endpoints included the following:

- ACR_{20} and ACR_{70} response rates at week 24
- ACR_{20}, ACR_{50}, and ACR_{70} response rates at week 12
- Sustained ACR_{20} response, defined as a positive response for ≥ 4 monthly measurements, with 1 occurring at month 6
- Percentage of subjects with good or moderate European League Against Rheumatism (EULAR) response at week 24
- Proportion of subjects who had ≥ 50% improvement over baseline at week 24 in the following measures:
    - Tender/painful joint count
    - Swollen joint count
    - Subject's functional status as measured by the HAQ

- Change and percent change from baseline at week 24 with respect to:
  - tender/painful joint count
  - swollen joint count
  - physician's global assessment of disease activity
  - subject's global assessment of disease activity
  - subject's assessment of pain
  - subject's functional status as measured by the HAQ
  - CRP
  - ESR
  - subject's duration of morning stiffness
  - disease activity score based on tender and swollen joint counts (28-joint count), ESR, and subject's global assessment (DAS28)
  - Health-related quality-of-life assessment (SF-36)

3. Safety Endpoints

Safety endpoints included the subject incidence rates of adverse events (including infections and malignancies) and laboratory assessments (change from baseline in hematology, chemistry, coagulation, autoimmune antibodies, urinalysis, and anti-anakinra and –etancercept antibodies).

4. Statistical Methods

a) General Approach

The evaluable efficacy subset was based on the modified intent-to-treat (M-ITT) population. It included all subjects who received at least 1 dose each of anakinra/placebo and etanercept/sham. Subjects in the M-ITT subset were analyzed according to their original randomized treatment, regardless of the actual treatment received during the study. The evaluable safety subset included all randomized subjects receiving at least 1 dose of either anakinra/placebo or etanercept/sham. Subjects without a valid value for a particular safety endpoint were excluded from the analysis of that endpoint.

The completer subset included all randomized subjects that completed the double-blind portion of the study. The same imputation method used in the primary analysis was used for subjects in the completer subset who had missing data. This subset was used in a sensitivity analysis to assess the robustness of the results from the M-ITT subsets.

b) Primary Analysis of the Primary Endpoint

The primary analysis was planned to compare the proportion of subjects who received anakinra + etanercept BIW who achieved an ACR_{50} response at week 24 with the proportion of subjects in the etanercept alone group who achieved that response. The evaluable efficacy subset was to include all subjects who received at least 1 dose each of anakinra/placebo and etanercept/sham. For this analysis, a logistic regression model was planned, with treatment group as a main effect.

c) Secondary Analysis of the Primary Endpoint

Secondary analyses of the primary endpoint were done with logistic regression (to evaluate the week-24 ACR_{50} response rates), adjusting for the following baseline covariates:

- Age
- Sex
- Race/ethnicity
- Rheumatoid factor
- Duration of RA (yrs)
- NSAID use
- Corticosteroid use
- Baseline ACR components
- Number of previous DMARDs
- Study center
- Renal function
- Body weight (kg)

Subjects with missing ACR scores were considered nonresponders. Secondary continuous variables were analyzed using a repeated measures mixed model.

d) Interim Analysis

An interim analysis was not performed for this study.

e) Safety Analyses

The safety subset included all randomized subjects receiving at least 1 dose of anakinra/placebo or etanercept/sham. Subjects' data were to appear in the safety tables according to the treatment that was assigned at randomization.

B. Study Population

The demographics and baseline characteristics of subjects who received study drug are described in **Table 16** and **Table 17.** In general, demographics at study entry were well-balanced across the treatment groups. 77% of the subjects were women, and 80% were white. The etanercept alone group had fewer Hispanic or Latino subjects (5%) than the combination treatment groups (approximately 15% each).

Table 16: Subject Demographics by Treatment Group

	Etanercept 25 mg BIW (N = 80)		Anakinra 100 mg QD		Etanercept 25 mg QW (N = 81)		Etanercept 25 mg BIW (N = 81)		Total (N = 242)	
Sex - n (%)										
Female	66	(83)			58	(72)	63	(78)	187	(77)
Male	14	(18)			23	(28)	18	(22)	55	(23)
Ethnic group - n (%)										
White or Caucasian	69	(86)			63	(78)	61	(75)	193	(80)
Black or African-American	4	(5)			5	(6)	2	(3)	11	(5)
Hispanic or Latino	4	(5)			13	(16)	12	(15)	29	(12)
Asian	2	(3)			0	(0)	2	(3)	4	(2)
Japanese	0	(0)			0	(0)	1	(1)	1	(<1)
American Indian or Alaska Native	1	(1)			0	(0)	1	(1)	2	(<1)
Native Hawaiian or Other Pacific Islander	0	(0)			0	(0)	0	(0)	0	(0)
Aborigine	0	(0)			0	(0)	0	(0)	0	(0)
Other	0	(0)			0	(0)	2	(3)	2	(<1)
Age (year)										
Mean	54.4				53.8		55.7		54.6	
Median	54.0				54.0		56.0		55.0	

N = Number of subjects randomized and received at least 1 dose of test article

The mean age of subjects was 55 years and the mean body weight was 79 kg. 80% of subjects had creatinine clearance rates > 80 mL/min, though at the lower range creatinine clearances, there was more variability between treatment groups.

Table 17: Baseline Characteristics

	Etanercept 25 mg BIW (N = 80)		Anakinra 100 mg QD		Etanercept 25 mg QW (N = 81)		Etanercept 25 mg BIW (N = 81)		Total (N = 242)	
Weight (kg)										
Mean	75.1				81.5		79.9		78.9	
Body mass index (kg/m^2)										
Mean	28				29		29		29	
Creatinine clearance[a] (mL/min) - n (%)										
< 30	0	(0)			0	(0)	0	(0)	0	(0)
30 - 50	1	(1)			1	(1)	6	(7)	8	(3)
> 50 - 80	16	(20)			10	(12)	14	(17)	40	(17)
> 80	62	(78)			70	(86)	61	(75)	193	(80)

N = Number of subjects randomized and received at least 1 dose of test article
n = Number of subjects with non-missing baseline data

Disease status measures at baseline are shown in **Table 18.** Subjects in all study groups demonstrated profiles that were similar and typical of the target RA population. The mean duration of disease was 10 years, and patients had a mean tender/painful joint count of 33 at baseline, a mean swollen joint count of 22, mean HAQ of 1.5, and a mean CRP level of 2.1 mg/dL.

Table 18: Disease Status Measures at Baseline

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81)	Etanercept 25 mg BIW (N = 81)	Total (N = 242)
Duration of rheumatoid arthritis (year)				
Mean	9.74	9.52	10.63	9.97
Median	7.50	5.89	7.20	6.84
Tender/painful joint count (0 - 68)				
Mean	31.01	30.95	35.93	32.64
Median	30.00	28.00	35.00	32.00
Swollen joint count (0 - 66)				
Mean	21.44	19.78	23.36	21.52
Median	20.50	19.00	22.00	20.00
Physician's assessment of disease activity (0 - 100)				
Mean	62.44	57.00	61.38	60.26
Median	66.50	59.00	65.00	64.00
Subject's assessment of disease activity (0 - 100)				
Mean	62.55	60.16	62.00	61.57
Median	67.00	63.00	63.00	65.00
Subject's assessment of pain activity (0 - 100)				
Mean	64.0	62.3	63.4	63.2
Median	68.5	66.0	65.0	65.0
Health assessment questionnaire (0 - 3)				
Mean	1.48	1.47	1.59	1.51
Median	1.50	1.50	1.63	1.50
C-reactive protein (mg/dL)[a]				
Mean	2.0	2.4	2.0	2.1
Median	1.2	1.6	1.0	1.1
Erythrocyte sedimentation rate (mm/hr)[b]				
Mean	44.6	49.2	49.9	47.9
Median	40.0	42.0	43.0	42.0
Duration of morning stiffness (min/day)				
Mean	145.3	154.4	159.5	153.1
Median	120.0	90.0	120.0	120.0

Table 18 (cont'd): Disease Status Measures at Baseline

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD + Etanercept 25 mg QW (N = 81)	Etanercept 25 mg BIW (N = 81)	Total (N = 242)
Subject's assessment of pain activity (0 - 100)				
Mean	64.0	62.3	63.4	63.2
Median	68.5	66.0	65.0	65.0
Health assessment questionnaire (0 - 3)				
Mean	1.48	1.47	1.59	1.51
Median	1.50	1.50	1.63	1.50
C-reactive protein (mg/dL)[a]				
Mean	2.0	2.4	2.0	2.1
Median	1.2	1.6	1.0	1.1
Erythrocyte sedimentation rate (mm/hr)[b]				
Mean	44.6	49.2	49.9	47.9
Median	40.0	42.0	43.0	42.0
Duration of morning stiffness (min/day)				
Mean	145.3	154.4	159.5	153.1
Median	120.0	90.0	120.0	120.0

Approximately half (49%) of patients had a history of corticosteroid use, and the majority (96%) used non-steroidal anti-inflammatory drugs, **Table 19**. The median methotrexate dose was 15 mg/wk and 40% of patients were already on one DMARD.

Table 19: RA Medication at Baseline

	Etanercept 25 mg BIW (N = 80)		Anakinra 100 mg QD (N = 81)		Etanercept 25 mg BIW (N = 81)		Total (N = 242)	
Corticosteroid use - n (%)	39	(49)	44	(54)	36	(44)	119	(49)
NSAIDs use - n (%)	77	(96)	77	(95)	78	(96)	232	(96)
MTX dose (mg/wk)								
Mean	16.09		16.15		15.71		15.98	
Median	15.00		15.00		15.00		15.00	
MTX dose (mg/wk) - n (%)								
< 10	0	(0)	0	(0)	3	(4)	3	(1)
10 - 14.9	20	(25)	21	(26)	25	(31)	66	(27)
15.0 - 19.9	40	(50)	35	(43)	27	(33)	102	(42)
20.0 - 25.0	20	(25)	25	(31)	26	(32)	71	(29)
> 25	0	(0)	0	(0)	0	(0)	0	(0)
Number of previous DMARDs - n (%)								
1	34	(43)	31	(38)	31	(38)	96	(40)
2	19	(24)	23	(28)	20	(25)	62	(26)
3	12	(15)	15	(19)	19	(24)	46	(19)
4	9	(11)	6	(7)	8	(10)	23	(10)
5+	6	(8)	6	(7)	3	(4)	15	(6)

N = Number of subjects randomized and received at least 1 dose of test article
n = Number of subjects with non-missing baseline data

C. Study Conduct

Study 2000223 was conducted at 41 US sites at which 242 subjects were randomized in a 1:1:1 fashion. 77% of subjects were women with a mean age of 55 years. 80% were White, 12% were Hispanic, and 5% were Black. The important inclusion criteria were:

- Disease duration of $\geq$ 24 weeks
- Active RA (defined as $\geq$ swollen joints, $\geq$ 9 tender/painful joints, and $\geq$ 2 of the following; morning stiffness $\geq$ 45 minutes, C-reactive protein $\geq$ 1.5 mg/dL, or ESR of $\geq$ 28 mm/hr
- Treated with MTX for $\geq$ 16 weeks, with a stable dosage at 10 to 25 mg/week for 8 weeks

The overall study design is presented in **Figure 2:** below:

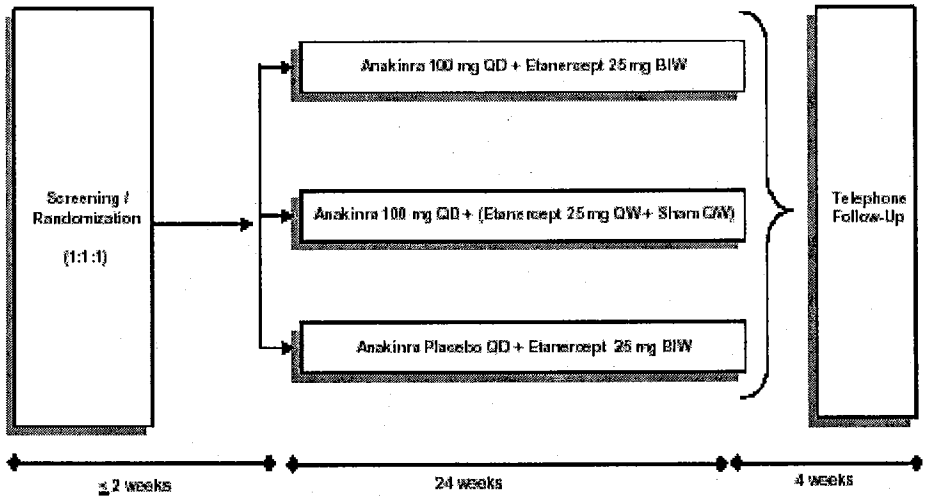


Figure 2: Study Schema for study #20000223

The study design was an active-controlled study. Because 2 different drugs with 3 treatment regimens were examined, it was necessary to administer the same number of injections to all subjects in order to maintain the study blind. Therefore, subjects who received etanercept QW were administered a sham injection in place of a second etanercept injection each week. In an attempt to minimize potential bias in the study, clothing was used to cover injection sites during assessments of signs and symptoms, since injection site reactions (ISRs) occur at an increased frequency relative to placebo. Independent assessors who were blinded to all other safety and efficacy assessments evaluated swollen and tender/painful joints. Additionally, postbaseline C-reative protein and erythrocyte sedimentation rate values for individual subjects were kept blinded to Immunex and study site personnel, as both anakinra and etanercept are known to affect these 2 acute phase reactants. A central laboratory [redacted] was responsible for laboratory analyses of hematology, serum chemistry, CRP, rheumatoid factor (RF), antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, serum pregnancy, and urinalysis. Approximately once a month, an internal safety monitoring committee (SMC) reviewed blinded aggregate safety data, including disposition, baseline demographics and characteristics; incidences of adverse events, serious adverse events, serious infectious episodes, and infectious episodes; and summary statistics for selected laboratory analytes. The results of the safety review remained blinded to all Immunex personnel directly involved with the conduct of the study. A Clinical Safety Specialist performed an on-going evaluation of blinded safety data collected during the course of the study for all subjects who received $\geq$ 1 dose of study drug. Any clinically significant safety findings were forwarded to the SMC, and results of any assessments which could be of

potential concern were communicated to the appropriate members of the GDT and to a clinician within the International Clinical Safety Department.

All efficacy, pharmacokinetic, and safety assessments were standard and generally accepted for studies of RA. The ACR_{50} response was chosen as the primary endpoint rather than the more typical ACR_{20} that was originally established to detect a clinically significant improvement in RA. The 20% level of patient improvement has proven useful in identifying active anti-RA therapies, but leaves substantial room for clinical improvement. The ACR_{50} response rate was chosen in order to evaluate whether the combination of etanercept and anakinra would provide not only a significant, but also a substantial, clinical response.

1. Subject Disposition

Table 20 displays the subject disposition for the study. A total of 244 subjects were enrolled in this study at 41 centers in the United States. Of 244 randomized subjects, 242 received study drug (1 subject in the etanercept alone treatment group withdrew consent and 1 subject in the anakinra + etanercept BIW combination treatment group was determined ineligible and never received study drug. A total of 204 subjects (84%) completed the study. Fewer patients completed six months of treatment in the 2 study arms receiving the combination of anakinra and etanercept (78% and 80%) than in the study arm receiving etanercept alone (93%).

Table 20: Subject Disposition

	Etanercept 25 mg BIW n (%)	Etanercept 25 mg QW n (%)	Anakinra 100 mg QD + Etanercept 25 mg BIW n (%)	Total n (%)
Subjects screened				362
Subjects randomized	81	81	82	244
Test Article Accounting				
Subjects who never received test article	1 (1)	0 (0)	1 (1)	2 (1)
Subjects who received test article	80 (99)	81 (100)	81 (99)	242 (99)
Subjects who completed test article	75 (93)	63 (78)	66 (80)	204 (84)
Subjects who discontinued test article	5 (6)	18 (22)	15 (18)	38 (16)
Study Completion Accounting				
Subjects who completed study	75 (93)	63 (78)	66 (80)	204 (84)
Subjects who discontinued study	6 (7)	18 (22)	16 (20)	40 (16)

Note: Percentages based on subjects randomized

2. Study Discontinuation

40 of 244 randomized patients (16%) discontinued the study. Across all treatment groups, withdrawal of consent was the most frequent reason for discontinuation from the study (**Table 21**) as well as the study drug (**Table 22**). A total of 18 (7%) subjects who received treatment withdrew consent: 13 (8%) of 163 subjects in the two combination treatment groups versus 4 (5%) of 81 subjects in the etanercept alone group. In addition, of the 13 patients who discontinued the study due to adverse events, all were assigned to the combination treatment groups. Other patients discontinued the study due to administrative reasons, being lost to follow up, etc., but these occurred in small numbers. One patient died during participation in the study, and one patient discontinued the study due to protocol deviations (both of these patients were assigned to the anakinra + etancercept BIW combination treatment arm).

Table 21: Study Discontinuation

		Anakinra 100 mg QD		
	Etanercept 25 mg BIW	Etanercept 25 mg QW	Etanercept 25 mg BIW	Total
	n (%)	n (%)	n (%)	n (%)
Subjects randomized	81	81	82	244
Subjects who completed study	75 (93)	63 (78)	66 (80)	204 (84)
Subjects who discontinued study	6 (7)	18 (22)	16 (20)	40 (16)
Ineligibility determined	0 (0)	1 (1)	1 (1)	2 (1)
Protocol deviation	0 (0)	0 (0)	1 (1)	1 (0)
Adverse event	0 (0)	7 (9)	6 (7)	13 (5)
Consent withdrawn	5 (6)	7 (9)	6 (7)	18 (7)
Administrative decision	1 (1)	0 (0)	0 (0)	1 (0)
Lost to follow-up	0 (0)	1 (1)	1 (1)	2 (1)
Death	0 (0)	0 (0)	1 (1)	1 (0)
Other	0 (0)	2 (2)	0 (0)	2 (1)

Note: Percentages based on subjects randomized

3. Reasons for Test Article Discontinuation

The number of patients who discontinued the study drug and the reasons why are presented in **Table 22**. 99% of all patients randomized received the test article, though there were notable differences in the number of patients who completed the test article. 93% of patients in the etanercept only treatment arm completed the test article compared to 78% and 80% in the combination etanercept QW and BIW treatment arms, respectively. The lower percentages of patients in the combination treatment arms who completed the test article can be accounted for by the number of patients who discontinued the study drug due to

an adverse event or due to withdrawn consent. 14 of 81 (17%) patients in the combination anakinra + etanercept QW arm and 13 of 82 (16%) patients in the combination anakinra + etanercept BIW arm discontinued the test article due to an AE or withdrawn consent, compared to 4 of 81 (5%) patients in the etanercept alone arm.

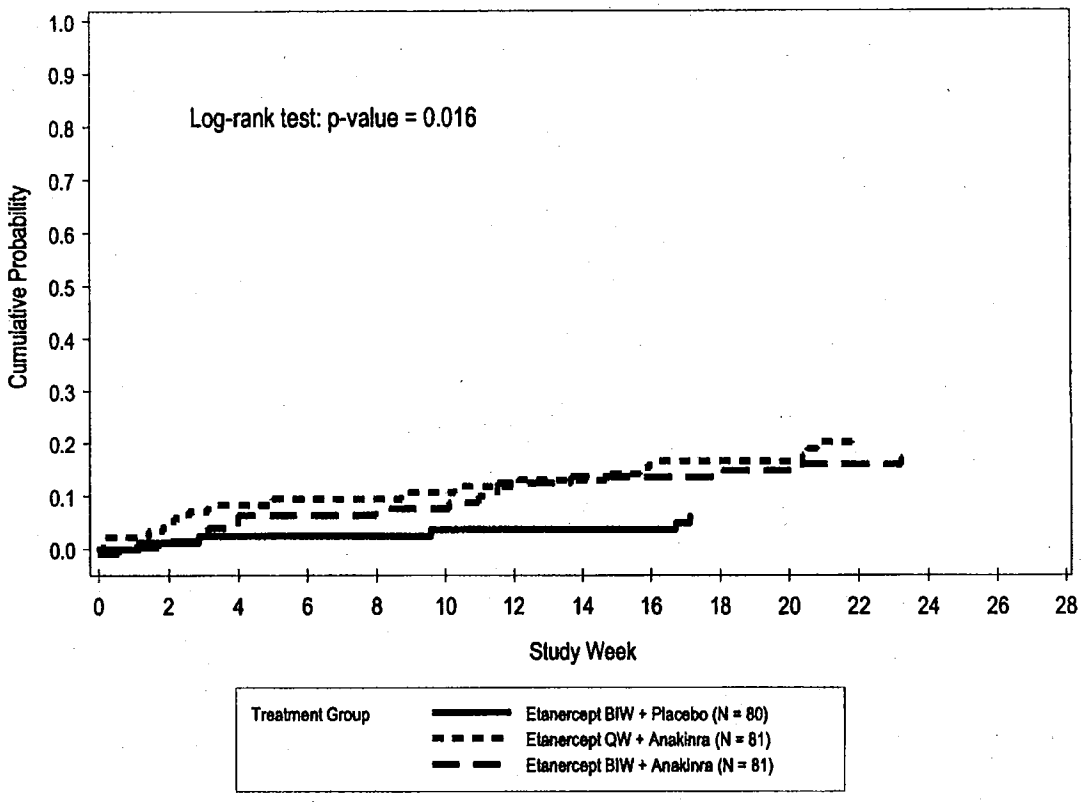
Table 22: Reason for Test Article Discontinuation

		Anakinra 100 mg QD		
	Etanercept 25 mg BIW n (%)	Etanercept 25 mg QW n (%)	Etanercept 25 mg BIW n (%)	Total n (%)
Subjects randomized	81	81	82	244
Subjects who never received test article	1 (1)	0 (0)	1 (1)	2 (1)
Subjects who received test article	80 (99)	81 (100)	81 (99)	242 (99)
Subjects who completed test article	75 (93)	63 (78)	66 (80)	204 (84)
Subjects who discontinued test article	5 (6)	18 (22)	15 (18)	38 (16)
Ineligibility determined	0 (0)	1 (1)	0 (0)	1 (0)
Protocol deviation	0 (0)	0 (0)	1 (1)	1 (0)
Adverse event	0 (0)	7 (9)	6 (7)	13(5)
Consent withdrawn	4 (5)	7 (9)	7 (9)	18(7)
Administrative decision	1 (1)	0 (0)	0 (0)	1 (0)
Lost to follow-up	0 (0)	1 (1)	0 (0)	1 (0)
Death	0 (0)	0 (0)	1 (1)	1 (0)
Subject request	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	2 (2)	0 (0)	2 (1)

Note: Percentages based on subjects randomized

A time to withdrawal analysis (**Figure 3**) indicated a difference between that of subjects in the etanercept alone group compared with subjects in the combination treatment groups. The cumulative probability of subject withdrawal remained relatively stable over time for the etanercept alone treatment group, and the last premature withdrawal was seen in this group at approximately week 17. In contrast, the cumulative probability of withdrawal gradually increased over time for the combination treatment groups, and withdrawals continued beyond week 20. Subject withdrawal rates in the combination (anakinra + etanercept QW and anakinra + etanercept BIW) treatment groups were higher than in the etanercept alone group (22% and 20% vs. 7%, respectively).

Figure 3: Time to Withdrawal From Study Drug



Two subjects discontinued the study for reasons coded under the heading "other": One withdrew because the study center closed, and 1 subject was withdrawn because she was unblinded to treatment. Both subjects were in the anakinra + etanercept QW combination treatment group. Two subjects withdrew before receiving study drug: A subject in the etanercept alone treatment group decided not to participate in the study after being randomized, and 1 subject randomized to anakinra + etanercept BIW was determined ineligible for the study due to prior exposure to a TNF inhibitor.

4. Protocol Deviations

Table 23 highlights subjects who had protocol deviations that had the potential to affect conclusions drawn from analysis of the primary endpoint of the study. A total of 39 (16%) subjects across all groups had such protocol deviations. Most deviations involved study drug (17 [7%] subjects), or were deviations from entry/eligibility criteria (11 [5%] subjects).

Table 23: Summary of Important Protocol Deviations

	Etanercept 25 mg BIW (N = 81)		Anakinra 100 mg QD: Etanercept 25 mg QW (N = 81)		Anakinra 100 mg QD: Etanercept 25 mg BIW (N = 82)		Total (N = 244)	
	n	%	n	%	n	%	n	%
Having at least one deviation	11	14	16	20	12	15	39	16
Deviation Description								
Study Drug	8	9	3	4	6	7	17	7
Deviations from entry/eligibility Criteria	2	3	6	7	3	4	11	5
Scheduled evaluation missing	2	3	3	4	1	1	6	3
Other treatment compliance	0	0	4	5	0	0	4	2
Termination criteria	0	0	1	1	2	2	3	1
Missing data	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Timing of tests and procedures	0	0	0	0	0	0	0	0
Exclusionary med/treatment	0	0	0	0	0	0	0	0

N = All randomized subjects

D. Efficacy Evaluation

1. Primary Endpoint

The primary endpoint of this study was the proportion of subjects achieving an ACR_{50} response at week 24. The clinical hypothesis was that combination treatment with anakinra and etanercept would provide a superior clinical effect in improving signs and symptoms of RA over treatment with etanercept alone. As shown in **Table 24** below, the observed week 24 ACR_{50} response rate in the anakinra + etanercept BIW treatment group was not significantly better than in the etanercept alone group. Thirty-one percent of subjects in the combined anakinra + etanercept BIW treatment group achieved an ACR_{50} response, compared with 41% of subjects in the etanercept alone treatment group, with an odds ratio of 0.64 (90% CI 0.37, 1.09) and a p-value of 0.914.

Table 24: Subjects Achieving an ACR_{50} Response at Week 24, Comparison with Etanercept BIW Monotherapy

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD + Etanercept 25 mg BIW (N = 81)
Number of Responders (%)	33 (41)	25 (31)
Odds Ratio		0.64
90% CI for Odds Ratio		(0.37, 1.09)
p-value		0.914

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to etanercept BIW monotherapy using a logistic regression 1-sided Wald test
Statistical significance level = 0.05
Subjects with missing ACR responses are considered to be ACR non-responders

Comparisons of BIW etanercept vs. QW treatment and etanercept alone were also performed. No statistically significant differences were observed between the ACR_{50} response rates of subjects treated QW with etanercept + anakinra and subjects treated BIW with etanercept, regardless of whether BIW treatment included anakinra (**Table 25**). These data do not support the hypothesis of this study, namely that combination therapy with BIW etanercept + anakinra would be more efficacious than etanercept alone or QW etancercept combination therapy.

The week-24 ACR_{50} response rates in the etanercept alone treatment group and in the anakinra + etanercept QW treatment group were 41% and 39%, respectively, versus 31% in the anakinra + etanercept BIW treatment group (**Table 25**). The odds ratio of subjects in the etanercept alone treatment group achieving an ACR_{50} response relative to the anakinra + etancercept QW treatment group was 1.11 (95%CI: 0.59, 2.09) with a (two-tailed) p-value of 0.747. For the comparison of subjects in the anakinra + etanercept BIW group relative to those in the anakinra + etanercept QW treatment group, the odds ratio was 0.71 (95% CI: 0.37, 1.35) with a 2-tailed p-value of 0.294.

Table 25: Subjects Achieving an ACR50 Response at Week 24, Comparison with Combination of Etanercept QW and Anakinra QD

	Etanercept 25mgBIW (N = 80)	Etanercept 25 mg QW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)
Number of Responders (%)	33 (41)	31 (39)	25 (31)
Odds Ratio	1.11		0.71
95% CI for Odds Ratio	(0.59, 2.09)		(0.37, 1.35)
p-value	0.747		0.294

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to combination of etanercept QW and anakinra QD using a logistic regression 2-sided Wald test
Statistical significance level = 0.05
Subjects with missing ACR responses are considered to be ACR non-responders

2. Secondary Analyses

Sensitivity analyses of ACR_{50} response rates at week 24 were performed using the completer subsets, which includes all randomized subjects who completed the 24-week treatment portion of the study. Results of the completer analyses were comparable to those of the primary analyses, showing no significant difference between the week-24 ACR_{50} response rates of subjects treated with anakinra + etanercept BIW and subjects treated with etanercept alone, (**Table 26**), nor between subjects treated with combination anakinra + etanercept BIW and subjects treated with anakinra + etanercept QW (**Table 27**).

Table 26: Subjects Achieving an ACR_{50} Response at Week 24 Based on Completer Subset Comparison with Etanercept BIW Monotherapy

	Etanercept 25mg BIW (N = 80)	Anakinra 100 mg QD + Etanercept 25 mg BIW (N = 81)
Completers	75	66
Number of Responders (%)	33 (44)	24 (36)
Odds Ratio		0.73
90% CI for Odds Ratio		(0.41, 1.28)
p-value		0.821

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to etanercept BIW monotherapy using a logistic regression 1-sided Wald test
Statistical significance level = 0.05
% = number of responders / completers
Subjects with missing ACR responses are considered to be ACR non-responders

Table 27: Subjects Achieving an ACR_{50} Response at Week 24 Based on Completer Subset Comparison with Combination of Etanercept QW and Anakinra QD

	Etanercept 25 mg BIW (N = 80)	Etanercept 25 mg QW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)
Completers	75	63	66
Number of Responders (%)	33 (44)	31 (49)	24 (36)
Odds Ratio	0.81		0.59
95% CI for Odds Ratio	(0.41, 1.59)		(0.29, 1.19)
p-value	0.541		0.142

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to combination of etanercept QW and anakinra QD using a logistic regression 2-sided Wald test
Statistical significance level = 0.05
% = number of responders / completers
Subjects with missing ACR responses are considered to be ACR non-responders

Similar results were seen in sensitivity analyses that adjusted for subjects who increased their DMARD or steroid use on or before week 24. For these analyses, subjects who received a new DMARD or increased their DMARD or corticosteroid dosage while on study were considered ACR non-responders. The adjusted ACR_{50} response rates for increases in DMARDs and steroid dose while on study were lower in the anakinra + etanercept BIW combination group (27%) compared to the etanercept alone (38%) and anakinra + etanercept QW (34%) groups **Table 28** and **Table 29.**

Table 28: Subjects Achieving an ACR_{50} Response at Week 24, Adjusting for Increases in DMARDs and Steroid Dose While on Study Comparison with Etanercept BIW Monotherapy

	Etanercept 25 mg BIW	Anakinra 100 mg QD + Etanercept 25 mg BIW
	(N = 80)	(N = 81)
Number of Responders (%)	30 (38)	22 (27)
Odds Ratio		0.62
90% CI for Odds Ratio		(0.35, 1.08)
p-value		0.919

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to etanercept BIW monotherapy using a logistic regression 1-sided Wald test
Statistical significance level = 0.05
Subjects who received new DMARD or increased DMARD or corticosteroids dosage while on study are considered to be ACR non-responders
Subjects with missing ACR responses are considered to be ACR non-responders

Table 29: Subjects Achieving an ACR_{50} Response at Week 24, Adjusting for Increases in DMARDs and Steroid Dose While on Study Comparison with Combination of Etanercept QW and Anakinra QD

	Etanercept 25 mg BIW (N = 80)	Etanercept 25 mg QW (N = 80)	Anakinra 100 mg QD / Etanercept 25 mg BIW (N = 81)
Number of Responders (%)	30 (38)	27 (34)	22 (27)
Odds Ratio	1.18		0.73
95% CI for Odds Ratio	(0.62, 2.26)		(0.37, 1.43)
p-value	0.621		0.364

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to combination of etanercept QW and anakinra QD using a logistic regression 2-sided Wald test
Statistical significance level = 0.05
Subjects who received new DMARD or increased DMARD or corticosteroids dosage while on study are considered to be ACR non-responders
Subjects with missing ACR responses are considered to be ACR non-responders

3. Sensitivity Analyses

Sensitivity analyses were also performed to assess the effects of various baseline covariates upon ACR_{50} response rates at week 24. No baseline covariate adjustments notably affected the rates. Results for comparison of BIW etanercept combination therapy with etanercept monotherapy (**Table 30**) and with QW etanercept combination treatment (**Table 31**) were unaffected by baseline covariate adjustments.

Table 30: Subjects Achieving an ACR_{50} Response at Week 24 -Adjusting for Baseline Covariates Comparison with Etanercept BIW Monotherapy

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD + Etanercept 25 mg BIW (N = 81)
Unadjusted		
Odds Ratio		0.64
p-value		0.914
Age		
Odds Ratio		0.65
p-value		0.900
Sex		
Odds Ratio		0.62
p-value		0.923
Race/ethnicity (caucasian/non-caucasian)		
Odds Ratio		0.63
p-value		0.915
Weight		
Odds Ratio		0.64
p-value		0.913
Rheumatoid factor positive		
Odds Ratio		0.55
p-value		0.960
Duration of RA		
Odds Ratio		0.65
p-value		0.901

Table 30: Subjects Achieving an ACR_{50} Response at Week 24 - Adjusting for Baseline Covariates, Comparison with Etanercept BIW Monotherapy (cont'd)

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD + Etanercept 25 mg BIW (N = 81)
NSAID use		
Odds Ratio		0.63
p-value		0.915
Corticosteroid use		
Odds Ratio		0.63
p-value		0.916
Tender/painful joint count		
Odds Ratio		0.73
p-value		0.827
Swollen joint count		
Odds Ratio		0.66
p-value		0.896
Physician's assessment of disease activity		
Odds Ratio		0.63
p-value		0.916
Patient's assessment of RA disease activity		
Odds Ratio		0.62
p-value		0.921
Patient's assessment of pain		
Odds Ratio		0.62
p-value		0.922
HAQ		
Odds Ratio		0.67
p-value		0.885
CRP (mg/dL)		
Odds Ratio		0.64
p-value		0.915
ESR (mm/hr)		
Odds Ratio		0.65
p-value		0.905
Creatinine clearance		
Odds Ratio		0.62
p-value		0.922
Number of previous DMARDs		
Odds Ratio		0.61
p-value		0.932

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to etanercept BIW monotherapy using a logistic regression 1-sided Wald test
Statistical significance level = 0.05
Subjects with missing ACR responses are considered to be ACR non-responders

Table 31: Subjects Achieving an ACR_{50} Response at Week 24, Adjusting for Baseline Covariates, Comparison with Combination of Etanercept QW and Anakinra QD

	Etanercept 25 mg BIW (N = 80)	Etanercept 25 mg QW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)
Unadjusted			
Odds Ratio	1.11		0.71
p-value	0.747		0.294
Age			
Odds Ratio	1.12		0.73
p-value	0.725		0.349
Sex			
Odds Ratio	1.16		0.72
p-value	0.649		0.330
Race/ethnicity (caucasian/non-caucasian)			
Odds Ratio	1.11		0.71
p-value	0.741		0.293
Weight			
Odds Ratio	1.10		0.70
p-value	0.774		0.281
Rheumatoid factor positive			
Odds Ratio	1.22		0.67
p-value	0.543		0.246
Duration of RA			
Odds Ratio	1.13		0.73
p-value	0.719		0.352
NSAID use			
Odds Ratio	1.10		0.70
p-value	0.769		0.280
Corticosteroid use			
Odds Ratio	1.10		0.70
p-value	0.760		0.283
Tender/painful joint count			
Odds Ratio	1.12		0.81
p-value	0.731		0.546
Swollen joint count			
Odds Ratio	1.15		0.76
p-value	0.662		0.411
Physician's assessment of disease activity			
Odds Ratio	1.13		0.72
p-value	0.699		0.321

Table 31 : Subjects Achieving an ACR_{50} Response at Week 24, Adjusting for Baseline Covariates Comparison with Combination of Etanercept QW and Anakinra QD (cont'd)

	Etanercept 25 mg BIW (N = 80)	Etanercept 25 mg QW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)
Patient's assessment of RA disease activity			
Odds Ratio	1.15		0.72
p-value	0.668		0.322
Patient's assessment of pain			
Odds Ratio	1.14		0.71
p-value	0.681		0.311
HAQ			
Odds Ratio	1.12		0.75
p-value	0.734		0.387
CRP (mg/dL)			
Odds Ratio	1.10		0.70
p-value	0.761		0.286
ESR (mm/hr)			
Odds Ratio	1.09		0.71
p-value	0.783		0.29
Creatinine clearance			
Odds Ratio	1.13		0.71
p-value	0.701		0.295
Number of previous DMARDs			
Odds Ratio	1.12		0.68
p-value	0.731		0.249

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to combination of etanercept QW and anakinra QD using a logistic regression 2-sided Wald test
Statistical significance level = 0.05
Subjects with missing ACR responses are considered to be ACR non-responders

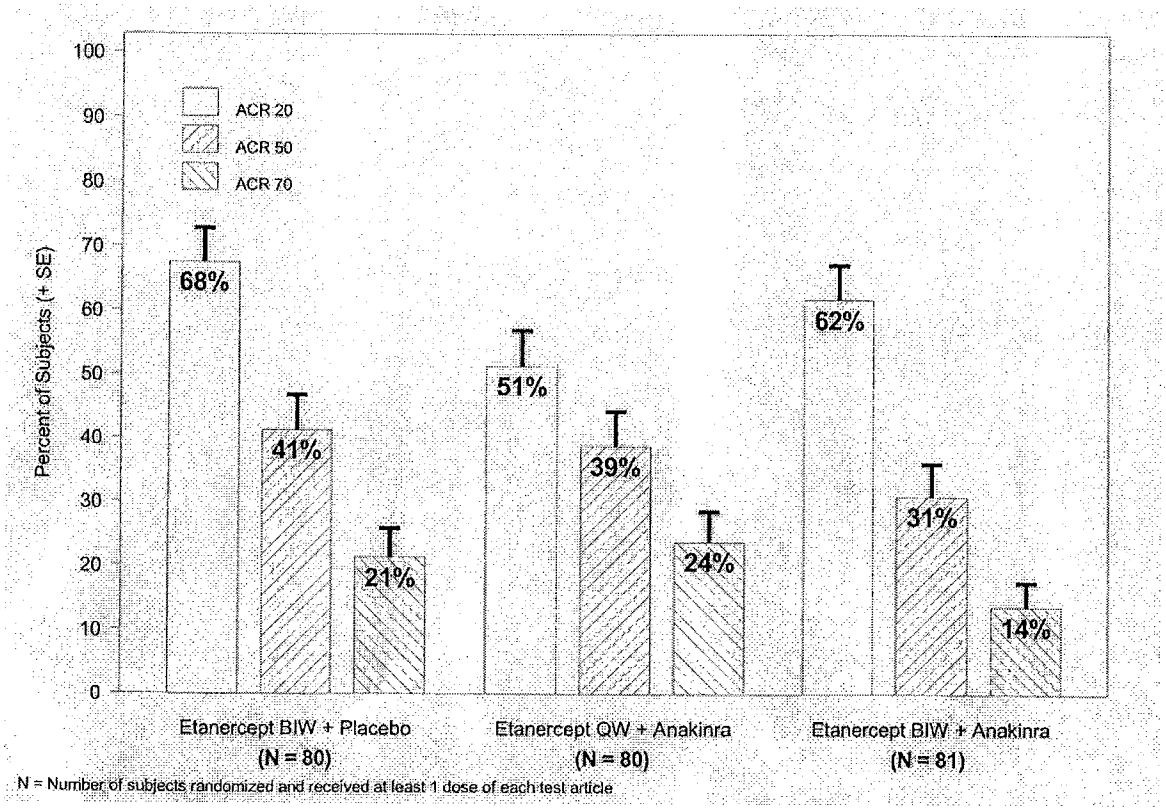
Secondary endpoints of study 20000223 included the week 24 ACR_{20} and ACR_{70} response rates. Patients randomized to the anakinra + etanercept BIW regimen had lower ACR_{20} and ACR_{70} response rates (62% and 14%) compared to those who received etanercept therapy alone (68% and 21%, respectively **Table 32**). These results are consistent with the primary endpoint (ACR_{50} response rates at week 24) and show no clinical benefit of adding anakinra to etanercept BIW in the treatment of rheumatoid arthritis.

Table 32: Subjects Achieving an ACR Response at Week 24 Comparison with Etanercept BIW Monotherapy

	Etanercept 25 mg BIW	Anakinra 100 mg QD + Etanercept 25 mg BIW
	(N = 80)	(N = 81)
ACR_{20}		
Number of Responders (%)	54 (68)	50 (62)
Odds Ratio		0.78
95% CI for Odds Ratio		(0.40, 1.48)
p-value		0.444
ACR_{70}		
Number of Responders (%)	17 (21)	11 (14)
Odds Ratio		0.58
95% CI for Odds Ratio		(0.25, 1.32)
p-value		0.202

N = Number of subjects randomized and received at least 1 dose of each test article
Odds ratio is a ratio of the odds of achieving an ACR response compared to etanercept BIW monotherapy using a logistic regression 2-sided Wald test
Statistical significance level = 0.05
Subjects with missing ACR responses are considered to be ACR non-responders

Figure 4: Percent of Subjects Achieving an ACR Response at Week 24



The ACR_{20}, ACR_{50}, and ACR_{70} response rates for each treatment group are shown in **Figure 4**. Comparison of the ACR_{20} response rates showed a significant difference between that of subjects treated with etanercept alone (68%) and subjects treated with anakinra + etanercept QW (51%). The odds ratio of subjects who received etanercept alone having an ACR_{20} response at week 24 relative to subjects who received anakinra + etanercept QW was 1.98 (95% CI: 1.05, 3.78), with a p-value of 0.037. No other treatment comparison demonstrated a significant difference between week-24 ACR_{20} response rates (p-values of likelihood ratio tests were $\geq$ 0.181).

E. Summary of Efficacy Evaluation

Overall, combination treatment with etanercept and anakinra showed no advantage in improving signs and symptoms of RA over treatment with etanercept alone. In fact, response rates were generally lower in patients receiving combination therapy than in those receiving etanercept alone. 31% of the anakinra + etanercept BIW treatment group achieved an ACR_{50} response at week 24 (the primary endpoint), compared with 41% in the etanercept alone treatment group, and 39% in the anakinra + etanercept QW treatment group. Analyses of the secondary endpoints showed that only the comparison for the week 24 ACR_{20} response rates of subjects treated with etanercept alone (68%) was statistically significant compared to those subjects treated with anakinra + etanercept QW (51%), (odds ratio 1.98; 95% CI: 1.05, 3.78; p=0.037).

F. Safety Evaluations

1. Deaths

One subject died in the anakinra + etanercept BIW treatment group during the study. The patient was a 70 y.o. woman with RA and a history of gastrointestinal ulcers who began receiving study drug in [redacted]. She was hospitalized for gastroenteritis (considered moderate) in [redacted]. Her last recorded dose of study drug was in [redacted] she was hospitalized with hypoxemia and diagnosed with **pneumonia**. The patient refused intubation, had a bronchoscopy performed which resulted in a pneumothorax, with **pulmonary fibrosis** noted on chest x-ray. The patient died [redacted] after hospital admission [redacted] with the cause of death determined to be acute respiratory failure due to pulmonary fibrosis. The investigator considered the events as possibly related to etanercept or anakinra treatment.

2. Serious Adverse Events

Table 33 displays the incidence of serious adverse events by body system and preferred term. 18 of 242 (7%) randomized subjects experienced SAEs. Most (16 of these 18 patients) were randomized to the combination treatment arms. The combination etanercept BIW arm had notably more patients reporting SAEs than the etanercept QW combination or etanercept alone arms (15% vs. 5% and 3%, respectively). Four of these subjects withdrew as a result of the events; all received combination treatment. Pneumonia and cellulitis were the only SAEs reported by > 1 subject (2 subjects each) and were reported only by subjects who received combination therapy. It is important to note that the SAEs experienced by 9 of the subjects in the combination treatment groups were serious infectious episodes, while no subjects in the etanercept alone group experienced a serious infectious episode. This is discussed in further detail under the Serious Infections section (below).

Table 33: Subject Incidence of Serious Adverse Events by Body System and Preferred Term

BODY SYSTEM Preferred Term	Etanercept 25 mg BIW (N = 80) n (%)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81) n (%)	Etanercept 25 mg BIW (N = 81) n (%)	Total (N = 242) n (%)
Number of Subjects Reporting Serious Adverse Events	2 (3)	4 (5)	12 (15)	18 (7)
BODY AS A WHOLE	0 (0)	0 (0)	1 (1)	1 (<1)
Pain Chest, Non-Cardiac	0 (0)	0 (0)	1 (1)	1 (<1)
CNS/PNS	0 (0)	0 (0)	2 (3)	2 (<1)
Cerebrovascular Disorder	0 (0)	0 (0)	1 (1)	1 (<1)
Neuralgia	0 (0)	0 (0)	1 (1)	1 (<1)
GASTROINTESTINAL	0 (0)	1 (1)	1 (1)	2 (<1)
Gastric Ulcer	0 (0)	1 (1)	0 (0)	1 (<1)
Gastroenteritis	0 (0)	0 (0)	1 (1)	1 (<1)
Hemorrhage GI	0 (0)	1 (1)	0 (0)	1 (<1)
HEART RATE/RHYTHM	1 (1)	0 (0)	0 (0)	1 (<1)
Arrhythmia Atrial	1 (1)	0 (0)	0 (0)	1 (<1)
HEMATOLOGIC	0 (0)	0 (0)	1 (1)	1 (<1)
Lymphoma Malignant	0 (0)	0 (0)	1 (1)	1 (<1)
MUSCULO-SKELETAL	0 (0)	0 (0)	1 (1)	1 (<1)
Pain Back	0 (0)	0 (0)	1 (1)	1 (<1)
MYO/ENDO/PERICARDIAL	0 (0)	0 (0)	1 (1)	1 (<1)
Pain Chest, Cardiac	0 (0)	0 (0)	1 (1)	1 (<1)

N = Number of subjects randomized and received at least 1 dose of test article

Table 33 (cont'd): Subject Incidence of Serious Adverse Events by Body System and Preferred Term

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)	Total (N = 242)
BODY SYSTEM Preferred Term	n (%)	n (%)	n (%)	n (%)
PSYCHIATRIC DISORDER	1 (1)	0 (0)	0 (0)	1 (<1)
Personality Disorder	1 (1)	0 (0)	0 (0)	1 (<1)
RESISTANCE MECHANISM	0 (0)	0 (0)	1 (1)	1 (<1)
Herpes Zoster	0 (0)	0 (0)	1 (1)	1 (<1)
RESPIRATORY	0 (0)	3 (4)	2 (3)	5 (2)
Dyspnea	0 (0)	1 (1)	0 (0)	1 (<1)
Pneumonia	0 (0)	1 (1)	2 (3)	3 (1)
Pneumonitis	0 (0)	1 (1)	0 (0)	1 (<1)
Pulmonary Fibrosis	0 (0)	0 (0)	1 (1)	1 (<1)
Respiratory Insufficiency	0 (0)	0 (0)	1 (1)	1 (<1)
SKIN AND APPENDAGES	0 (0)	1 (1)	2 (3)	3 (1)
Cellulitis	0 (0)	1 (1)	2 (3)	3 (1)
URINARY DISORDERS	0 (0)	0 (0)	1 (1)	1 (<1)
Pyelonephritis	0 (0)	0 (0)	1 (1)	1 (<1)
VASCULAR DISORDERS	0 (0)	0 (0)	1 (1)	1 (<1)
Transient Ischemic Attack	0 (0)	0 (0)	1 (1)	1 (<1)

N = Number of subjects randomized and received at least 1 dose of test article

3. Special Adverse Event Topics

a) Infections

Table 34 shows the incidence of infectious episodes by body system and preferred term for all randomized patients. The percentage of patients in the group receiving anakinra + etanercept BIW with infections was 47%, which is higher than the 40% of patients in the etanercept BIW alone group. Individual infections occurring at a higher rate in the anakinra + etanercept BIW arm compared to the etanercept BIW alone arm included genital moniliasis (3% vs. 1%), bronchitis (4% vs. 1%), respiratory tract infection (3% vs. 0%), pneumonia (4% vs. 0%), cellulitis (3% vs. 0%), wound infection (3% vs. 0%), cystitis (3% vs. 0%), and conjunctivitis (3% vs. 0%).

Table 34: Subject Incidence of Infectious Episodes by Body System and Preferred Term

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)	Total (N = 242)
BODY SYSTEM Preferred Term	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Infectious Episodes Adverse Events	32 (40)	30 (37)	38 (47)	100 (41)
APPLICATION SITE	0 (0)	1 (1)	0 (0)	1 (<1)
Injection Site Pain	0 (0)	1 (1)	0 (0)	1 (<1)
BODY AS A WHOLE	2 (3)	2 (3)	1 (1)	5 (2)
Influenza-Like Symptoms	2 (3)	1 (1)	1 (1)	4 (2)
Rigors	0 (0)	1 (1)	0 (0)	1 (<1)
GASTROINTESTINAL	2 (3)	3 (4)	4 (5)	9 (4)
Abscess Oral	2 (3)	0 (0)	0 (0)	2 (<1)
Esophagitis Fungal	0 (0)	1 (1)	0 (0)	1 (<1)
Gastroenteritis	0 (0)	0 (0)	1 (1)	1 (<1)
Gastroenteritis Viral	0 (0)	1 (1)	0 (0)	1 (<1)
Gingivitis	0 (0)	0 (0)	1 (1)	1 (<1)
Moniliasis Oral	0 (0)	0 (0)	1 (1)	1 (<1)
Tooth Disorder	0 (0)	0 (0)	1 (1)	1 (<1)
Vomiting	0 (0)	1 (1)	1 (1)	2 (<1)
HEARING/VESTIBULAR	3 (4)	5 (6)	2 (3)	10 (4)
Earache	0 (0)	0 (0)	1 (1)	1 (<1)
Otitis	2 (3)	4 (5)	1 (1)	7 (3)
Otitis Media	1 (1)	1 (1)	0 (0)	2 (<1)
HEMATOLOGIC	0 (0)	2 (3)	0 (0)	2 (<1)
Lymphadenopathy	0 (0)	2 (3)	0 (0)	2 (<1)
MUSCULO-SKELETAL	2 (3)	1 (1)	0 (0)	3 (1)
Arthralgia	1 (1)	1 (1)	0 (0)	2 (<1)
Bursitis	1 (1)	0 (0)	0 (0)	1 (<1)

Table 34 (cont'd) : Subject Incidence of Infectious Episodes by Body System and Preferred Term

BODY SYSTEM Preferred Term	Etanercept 25 mg BIW (N = 80) n (%)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81) n (%)	Etanercept 25 mg BIW (N = 81) n (%)	Total (N = 242) n (%)
REPRODUCTIVE	2 (3)	1 (1)	3 (4)	6 (3)
Leukorrhea	0 (0)	0 (0)	1 (1)	1 (<1)
Moniliasis Genital	1 (1)	0 (0)	2 (3)	3 (1)
Vaginitis	0 (0)	1 (1)	0 (0)	1 (<1)
Vaginitis Bacterial	1 (1)	0 (0)	0 (0)	1 (<1)
RESISTANCE MECHANISM	5 (6)	6 (7)	4 (5)	15 (6)
Herpes Simplex	2 (3)	2 (3)	1 (1)	5 (2)
Herpes Zoster	0 (0)	1 (1)	1 (1)	2 (<1)
Infection	2 (3)	2 (3)	1 (1)	5 (2)
Infection Fungal	2 (3)	1 (1)	0 (0)	3 (1)
Infection Viral	0 (0)	1 (1)	1 (1)	2 (<1)
RESPIRATORY	18 (23)	18 (22)	23 (28)	59 (24)
Allergic Rhinitis	0 (0)	1 (1)	0 (0)	1 (<1)
Bronchitis	1 (1)	3 (3)	3 (4)	7 (3)
Infection Respiratory Tract	0 (0)	1 (1)	2 (3)	3 (1)
Infection Upper Respiratory	11(14)	8 (10)	10 (12)	29 (12)
Infection Upper Respiratory, Viral	1 (1)	1 (1)	0 (0)	2 (<1)
Pharyngitis	0 (0)	0 (0)	1 (1)	1 (<1)
Pneumonia	0 (0)	3 (4)	3 (4)	6 (3)
Pneumonitis	0 (0)	1 (1)	0 (0)	1 (<1)
Respiratory Disorder	0 (0)	0 (0)	1 (1)	1 (<1)
Sinusitis	6 (8)	4 (5)	4 (5)	14 (6)
Sore Throat	0 (0)	0 (0)	1 (1)	1 (<1)
Upper Respiratory Tract Congestion	0 (0)	1 (1)	0 (0)	1 (<1)
SKIN AND APPENDAGES	2 (3)	2 (3)	6 (7)	10 (4)
Cellulitis	0 (0)	1 (1)	2 (3)	3 (1)
Dermatitis Fungal	0 (0)	0 (0)	1 (1)	1 (<1)
Paronychia	1 (1)	1 (1)	1 (1)	3 (1)
Rash	1 (1)	0 (0)	0 (0)	1 (<1)
Skin Ulceration	0 (0)	1 (1)	0 (0)	1 (<1)
Wound	0 (0)	0 (0)	2 (3)	2 (<1)
URINARY DISORDERS	8 (10)	3 (4)	8 (10)	19 (8)
Cystitis	0 (0)	1 (1)	2 (3)	3 (1)
Infection Urinary Tract	8 (10)	2 (3)	5 (6)	15 (6)
Pyelonephritis	0 (0)	0 (0)	1 (1)	1 (<1)
VISION DISORDERS	0 (0)	1 (1)	4 (5)	5 (2)
Allergic Conjunctivitis	0 (0)	0 (0)	1 (1)	1 (<1)
Cataract	0 (0)	0 (0)	1 (1)	1 (<1)
Conjunctivitis	0 (0)	1 (1)	2 (3)	3 (1)

N = Number of subjects randomized and received at least 1 dose of test article

b) Serious Infections

Serious infectious episodes were experienced by 9 (6%) of 162 subjects (**Table 35**) in the combination treatment groups (6 of 81 [7%] subjects in the anakinra + etanercept BIW treatment group, 3 of 81 [4%] in the anakinra + etanercept QW treatment group) and 0 subjects in the etanercept alone treatment group. Three of these subjects consequently withdrew from the study. No cases of tuberculosis were reported, though one case of disseminated herpes zoster was reported. Serious infectious episodes occurred after an average of 2 months exposure to combination treatment. The mean age of subjects who experienced serious infectious events was 60 years. Serious infectious episodes of cellulitis, pyelonephritis, and pneumonia led to the withdrawal of 1 subject each.

Table 35: Subject Incidence of Serious Infectious Episodes by Body System and Preferred Term

		Anakinra 100 mg QD		
	Etanercept 25 mg BIW (N = 80)	Etanercept 25 mg QW (N = 81)	Etanercept 25 mg BIW (N = 81)	Total (N = 242)
BODY SYSTEM Preferred Term	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Adverse Events	0 (0)	3 (4)	6 (7)	9 (4)
RESISTANCE MECHANISM	0 (0)	0 (0)	1 (1)	1 (0.4)
Herpes Zoster	0 (0)	0 (0)	1 (1)	1 (0.4)
RESPIRATORY	0 (0)	2 (3)	2 (3)	4 (3)
Pneumonia	0 (0)	1 (1)	2 (3)	3 (1)
Pneumonitis	0 (0)	1 (1)	0 (0)	1 (<1)
SKIN AND APPENDAGES	0 (0)	1 (1)	2 (3)	3 (1)
Cellulitis	0 (0)	1 (1)	2 (3)	3 (1)
URINARY DISORDERS	0 (0)	0 (0)	1 (1)	1 (<1)
Pyelonephritis	0 (0)	0 (0)	1 (1)	1 (<1)

N = Number of subjects randomized and received at least 1 dose of test article

c) Serious Infection Listings

Listed below are the diagnoses of the 9 (6%) of 162 subjects who experienced serious infectious episodes, all from the combination treatment groups:
Subject 22300103: cellulitis in the left arm
Subject 22300802: cellulitis in the left leg
Subject 22301501: disseminated herpes zoster
Subject 22302011: death due to respiratory failure, pneumonia, pulmonary fibrosis
Subject 22302013: pneumonia
Subject 22303101: E. coli pyelonephritis
Subject 22303102: bilateral lower extremity cellulitis
Subject 22303208: interstitial pneumonitis
Subject 22303406: bilateral pneumonia with neutropenia

d) Malignancies

Neoplasms were diagnosed in 6 (3%) of 242 subjects during the study though none were judged to be related to the study drug, (**Table 36**). 5 of 6 neoplasms were considered benign, with 2 out of 6 cases judged to be of moderate or severe severity. One of 6 patients developed malignant lymphoma, the only serious neoplasm in the study. This patient was a 71-year-old male who was in the anakinra + etanercept BIW treatment group diagnosed with malignant lymphoma approximately 21 weeks after starting the study.

Table 36: Subject Listings of Neoplasms Occurring in Study 20000223

Body System	Verbatim Term	Treatment Group	Severity	Related to Test Article?	Serious?
Body as a Whole	Cholesteatoma R ear	Etanercept BIW + placebo	2	No	No
Gastrointestinal	Colon polyp, benign	Etanercept BIW + placebo	1	No	No
Reproductive	Left breast lump	Etanercept BIW + placebo	1	No	No
Reproductive	Breast lump	Etanercept BIW + placebo	1	No	No
Skin and appendages	Basal cell Carcinoma (thigh)	Etanercept BIW + anakinra	1	No	No
Hematologic	Lymphoma	Etanercept BIW + anakinra	3	No	Yes

1= mild, 2=moderate, 3=severe, 4=life-threatening, 5= fatal

4. All Adverse Events

A total of 225 (93%) of 242 randomized subjects reported adverse events during the study (**Table 37**). The proportion of subjects reporting adverse events was similar for each treatment group, ranging from 90% to 95%. However, the combination treatment arms were associated with a higher overall incidence of some categories of adverse events than treatment with etanercept alone. 69% of patients from the combination groups had application site AEs compared to 40% in the etanercept alone group. Under the **application site body system**, more patients in the combination etanercept groups (35% and 28%) had **injection site erythema** compared to the etanercept alone group (9%). **Injection site pruritus** occurred in 25% and 26% of patients in the combination groups compared to 3% in the etanercept alone arm. **Injection site rash** occurred in 19% and 11% of combination treatment groups vs. 6% in the etanercept alone arm. **Injection site inflammation** occurred in 7% and 9% of combination treatment groups vs. 1% in the etanercept alone arm. Patients in the combination treatment groups also had more AEs reported under the **skin and appendages** body system compared to patients in the etanercept alone arm (24% and 26% compared to 14%, respectively). Lastly, 6% and 10% of patients in the combination etanercept treatment arms reported adverse events listed under **vision disorders**, compared to 1% of patients in the etanercept alone group.

Table 37: Subject Incidence of Adverse Events Occurring in ≥ 5% of Subjects by Body System and Preferred Term

	Etanercept 25mgBIW (N = 80)		Anakinra100 mg QD Etanercept 25 mg QW (N = 81)		Etanercept 25 mg BIW (N = 81)		Total (N = 242)	
BODY SYSTEM Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Number of Subjects Reporting Adverse Events	72	90%	77	95%	76	94%	225	93%
APPLICATION SITE	32	(40)	55	(68)	57	(70)	144	(60)
Injection Site Erythema	7	(9)	28	(35)	23	(28)	58	(24)
Injection Site Ecchymosis	19	(24)	10	(12)	17	(21)	46	(19)
Injection Site Pruritus	2	(3)	20	(25)	21	(26)	43	(18)
Injection Site Pain	13	(16)	12	(15)	9	(11)	34	(14)
Injection Site Rash	5	(6)	15	(19)	9	(11)	29	(12)
Injection Site Inflammation	1	(1)	6	(7)	7	(9)	14	(6)
RESPIRATORY	30	(38)	28	(35)	29	(36)	87	(36)
Infection Upper Respiratory	16	(20)	9	(11)	11	(14)	36	(15)
Sinusitis	7	(9)	5	(6)	5	(6)	17	(7)
BODY AS A WHOLE	25	(31)	19	(24)	24	(30)	68	(28)
Edema Peripheral	4	(5)	5	(6)	3	(4)	12	(5)
GASTROINTESTINAL	19	(24)	21	(26)	26	(32)	66	(27)
Nausea	7	(9)	10	(12)	8	(10)	25	(10)
Diarrhea	6	(8)	8	(10)	6	(7)	20	(8)
Vomiting	2	(3)	3	(4)	7	(9)	12	(5)
MUSCULO-SKELETAL	18	(23)	18	(22)	26	(32)	62	(26)
Arthritis Rheumatoid	5	(6)	6	(7)	6	(7)	17	(7)
Pain Back	2	(3)	3	(4)	9	(11)	14	(6)
SKIN AND APPENDAGES	11	(14)	19	(24)	21	(26)	51	(21)
CNS/PNS	14	(18)	16	(20)	20	(25)	50	(21)
Headache	8	(10)	8	(10)	6	(7)	22	(9)
URINARY DISORDERS	10	(13)	4	(5)	9	(11)	23	(10)
Infection Urinary Tract	8	(10)	3	(4)	5	(6)	16	(7)
HEMATOLOGIC	6	(8)	5	(6)	6	(7)	17	(7)
RESISTANCE MECHANISM	5	(6)	6	(7)	6	(7)	17	(7)
METABOLIC/NUTRITION	2	(3)	8	(10)	4	(5)	14	(6)
VISION DISORDERS	1	(1)	5	(6)	8	(10)	14	(6)

N = Number of subjects randomized and received at least 1 dose of test article
n = Number of subjects reporting at least 1 occurrence of an adverse event

A summary of the adverse events incidents is presented in **Table 38.** 8% of patients from both combination therapy groups had adverse events that led to withdrawal from the study, compared to 0% in the etanercept alone group. 10% of patients in the combination therapy groups had serious adverse events compared to 3% in the etanercept alone group. A total of 4 patients (3%) in the combination groups had SAEs leading to withdrawal from the study, compared to 0% in the etanercept alone group. In addition, the one death in the study occurred in the anakinra + etanercept BIW group. Serious infectious episodes (defined as those necessitating hospitalization or antibiotics) occurred in 9 of 162 (6%) patients in the combination therapy groups compared to 0 of 80 (0%) in the etanercept alone group. No serious infectious episodes in any treatment group resulted in death. The overall rate of infectious episodes was higher in the group receiving anakinra + etanercept BIW (47%) than in the group receiving etanercept BIW alone (40%), **Table 38.**

Table 38: Summary of Subject Incidence of Adverse Events

n (%)	Etanercept BIW (N = 80)	Combination Therapy: Etanercept QW + Anakinra QD (N = 81)	Combination Therapy: Etanercept BIW + Anakinra QD (N = 81)	All Combination Therapies (N = 162)
Adverse Events[a]	72 (90)	77 (95)	76 (94)	153 (94)
Leading to withdrawal	0 (0)	7 (9)	6 (7)	13 (8)
Injection Site Reaction	32 (40)	55 (68)	57 (70)	112 (69)
Serious Adverse Events[a]	2 (3)	4 (5)	12 (15)	16 (10)
Leading to withdrawal	0 (0)	1 (1)	3 (4)	4 (3)
Death	0 (0)	0 (0)	1 (1)	1 (<1)
Serious Infectious Episodes	0 (0)	3 (4)	6 (7)	9 (6)
Leading to withdrawal	0 (0)	1 (1)	2 (3)	3 (2)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Infectious Episodes	32 (40)	30 (37)	38 (47)	68 (42)
Leading to withdrawal	0 (0)	2 (3)	2 (3)	4 (3)
Resulting in antibiotic taken or hospitalization	0 (0)	3 (4)	6 (7)	9 (6)

N = Number of subjects randomized and received at least 1 dose of test article
[a] Includes infectious episodes

5. Withdrawals Due to Adverse Events

Adverse events led to the withdrawal of 13 of 242 (5%) subjects from the test articles, all of whom received combination treatment with anakinra and etanercept (**Table 39**). Events involving the application site were the most common adverse events resulting in test article withdrawal which accounted for 5 (2%) subjects. The only AEs causing the withdrawal of > 1 subject were injection site urticaria (3 subjects) and pneumonia (2 subjects), both occurring in the combination anakinra + etanercept QW group. No infectious episode resulted in study withdrawal in the etanercept alone group. In contrast, the combination therapy arms had 4 patients (3%) with infectious episodes that resulted in study withdrawal.

Table 39: Subject Incidence of Adverse Events Resulting in Withdrawal from Test Articles by Body System and Preferred Term

	Etanercept 25 mg BIW (N = 80)	Anakinra 100 mg QD Etanercept 25 mg QW (N = 81)	Anakinra 100 mg QD Etanercept 25 mg BIW (N = 81)	Total (N = 242)
BODY SYSTEM Preferred Term	n (%)	n (%)	n (%)	n (%)
Number of Subjects Reporting Adverse Events	0 (0)	7 (9)	6 (7)	13 (5)
APPLICATION SITE	0 (0)	3 (4)	2 (3)	5 (2)
Injection Site Erythema	0 (0)	1 (1)	0 (0)	1 (<1)
Injection Site Inflammation	0 (0)	0 (0)	1 (1)	1 (<1)
Injection Site Pain	0 (0)	1 (1)	0 (0)	1 (<1)
Injection Site Rash	0 (0)	1 (1)	0 (0)	1 (<1)
Injection Site Urticaria	0 (0)	2 (3)	1 (1)	3 (1)
BODY AS A WHOLE	0 (0)	1 (1)	0 (0)	1 (0)
Edema	0 (0)	1 (1)	0 (0)	1 (0)
HEARING/VESTIBULAR	0 (0)	1 (1)	0 (0)	1 (0)
Otitis	0 (0)	1 (1)	0 (0)	1 (0)
METABOLIC/NUTRITION	0 (0)	1 (1)	0 (0)	1 (<1)
SGOT Increased	0 (0)	1 (1)	0 (0)	1 (<1)
SGPT Increased	0 (0)	1 (1)	0 (0)	1 (<1)
MUSCULO-SKELETAL	0 (0)	0 (0)	1 (1)	1 (<1)
Arthralgia	0 (0)	0 (0)	1 (1)	1 (<1)
MYO/ENDO/PERICARDIAL	0 (0)	0 (0)	1 (1)	1 (<1)
Pain Chest, Cardiac	0 (0)	0 (0)	1 (1)	1 (<1)
RESPIRATORY	0 (0)	2 (3)	0 (0)	2 (<1)
Pneumonia	0 (0)	2 (3)	0 (0)	2 (<1)
SKIN AND APPENDAGES	0 (0)	1 (1)	1 (1)	2 (<1)
Cellulitis	0 (0)	0 (0)	1 (1)	1 (<1)
Urticaria	0 (0)	1 (1)	0 (0)	1 (<1)
URINARY DISORDERS	0 (0)	0 (0)	1 (1)	1 (<1)
Pyelonephritis	0 (0)	0 (0)	1 (1)	1 (<1)

N = Number of subjects randomized and received at least 1 dose of test article

6. Laboratory Evaluations

4 subjects in this study (**Table 40**) had Grade $\geq$ 2 shifts in WHO toxicity criteria in the total neutrophil count at some point in the study. Using a definition of neutropenia as a neutrophil count of $< 1.0 \times 10^9/L$ (discussed earlier in the Clinical Laboratory Evaluation section in study 20000125), 2 out of these 4 subjects in this study experienced neutropenia. Both of these patients received anakinra + etanercept BIW.

Table 40: Total Neutrophils Shifts From Baseline in WHO Toxicity Grades

		Most Extreme On-Study Grade											
Treatment Group	Baseline Grade	Increase						Decrease					
		N/A	0	1	2	3	4	N/A	0	1	2	3	4
Etanercept BIW + Placebo (N = 80)	N/A							-	-	-	-	-	-
	0							1	76	3	-	-	-
	1			Not Applicable				-	-	-	-	-	-
	2							-	-	-	-	-	-
	3							-	-	-	-	-	-
	4							-	-	-	-	-	-
Etanercept QW + Anakinra (N = 81)	N/A							-	-	-	-	-	-
	0							3	67	10	1	-	-
	1			Not Applicable				-	-	-	-	-	-
	2							-	-	-	-	-	-
	3							-	-	-	-	-	-
	4							-	-	-	-	-	-
Etanercept BIW + Anakinra (N = 81)	N/A							-	-	-	-	-	-
	0							3	59	16	3	-	-
	1			Not Applicable				-	-	-	-	-	-
	2							-	-	-	-	-	-
	3							-	-	-	-	-	-
	4							-	-	-	-	-	-

N = Number of subjects who received at least 1 dose of study drug.
N/A = Not available.

G. Summary of Safety Evaluation

The totality of the safety data thus presented indicate safety concerns regarding the use of combination anakinra + etanercept therapy in rheumatoid arthritis. While the proportion of patients having adverse events in each treatment group were comparable, the incidence of some noteworthy adverse events (namely one death, one malignancy, serious adverse events, serious infections, withdrawals due to adverse events, etc.) was higher in the combination anakinra + etanercept BIW arm compared to the etanercept alone arm. First, the study's one death and one case of malignant neoplasm (lymphoma) both occurred in the anakinra + etanercept BIW arm. Serious adverse events occurred more frequently in patients randomized to the combination etanercept BIW arm; the two SAE's reported by > 1 patient (pneumonia and cellulitis) occurred in the combination etanercept BIW arm. Additionally, serious infections occurred in a higher proportion of patients in the combination etanercept BIW arm, and the number of infections in this treatment arm was also higher than the other arms. All patients who discontinued the test article due to adverse events were randomized to one of the combination anakinra + etanercept treatment groups whereas no patient in the etanercept alone group discontinued the test article. Lastly, the two cases of neutropenia occurred in the combination etanercept BIW group.

H. Discussion of Study 20000223 Results

The study was adequately designed to investigate the sponsor's hypothesis that combination anakinra + etanercept therapy would result in a higher proportion of patients achieving a clinically meaningful response. However, the efficacy data from this study do not demonstrate any clinical benefit for patients receiving combination anakinra + etanercept therapy compared to those receiving etanercept alone in patients with active RA. The safety profile of combination anakinra + etanercept BIW therapy is poor, with a similar incidence of serious infections (7%) in this study compared to the earlier Phase 2 study #20000125 in this review which also examined the adverse event rate in combination therapy. Likewise, the tolerability of anakinra + etanercept combination treatment is poor, with more injection site reactions and more adverse events leading to withdrawal from the study compared to the etanercept alone group. In conclusion, the efficacy and safety data make the risk:benefit ratio of combination anakinra + etanercept therapy in RA unfavorable in clinical use.