SYNOPSIS

Name of the Sponsor: Amgen Inc. Thousand Oaks, CA	**Name of Finished Product:** Kineret® (anakinra)	**Name of Active Ingredient:** Recombinant-methionyl Human Interleukin-1 Receptor Antagonist (r-metHuIL-1ra)
Title of Study: A Multicenter, Double-blind, Randomized, Placebo-Controlled Study to Estimate the Effect of Anakinra (r-metHuIL-1ra) on Vaccine Antibody Response in Subjects with Rheumatoid Arthritis		
Investigator(s) and Study Center(s): Multi-center clinical trial conducted at 25 sites in United States and Canada.		
Publication(s): No publications have been prepared from the results of this study.		
Study Period: 20 August 2001 through 6 November 2003		**Development Phase:** 4
Introduction and Objectives: Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune, inflammatory disease of unknown etiology. Symptoms including joint stiffness, pain and swelling, fatigue and weakness, and psychological depression. Interleukin-1 (IL-1) is a key mediator of immune and inflammatory responses and has been implicated in the etiology of RA in animal models and RA patient studies. Anakinra, a competitive antagonist of IL-1 receptors, has been approved for the treatment of RA. *Primary Study Objective:* To estimate the effect of anakinra, 100 mg once daily (QD), on the development of an anti-tetanus response in subjects with rheumatoid arthritis, after vaccination with a tetanus and diphtheria toxoids injection. *Secondary Study Objective:* To evaluate the general safety profile of therapy with anakinra, 100 mg QD, in subjects with RA after vaccination with a tetanus and diphtheria toxoids injection.		
Methodology: This was a double-blind, placebo-controlled study in which subjects were randomly assigned to anakinra or placebo treatment, stratified by concomitant methotrexate administration. Subjects received daily subcutaneous (SC) injections of anakinra (100 mg QD) or placebo for 8 weeks, with tetanus/diphtheria toxoids injections administered at week 4. Antibody levels and titers of tetanus toxoid were evaluated at weeks 4 and 8. Subjects received their first SC injection at the study site, where investigators taught them the correct procedure for self-injection; thereafter, subjects administered their own injections. All adverse events were reported and assessed with regard to severity, seriousness, and relation to treatment. Serum anti-anakinra antibody levels were determined at week 8.		
Number of Subjects Planned: 144 (72 per treatment group)		

Number of Subjects Enrolled: 126 randomized (63 Anakinra, 63 Placebo)
Sex: 34 (27.0%) men, 92 (73.0%) women
Age: Mean = 55.0 years, SD = 10.86, Min/Max = 26/74 years
Ethnicity (Race): White/Caucasian = 97 (77.0%), Black/African-American = 14 (11.1%), Hispanic/Latino = 9 (7.1%), Asian = 4 (3.2%), American Indian or Alaska Native = 1 (0.8%), Aborigine = 1 (0.8%)

Treatment	Sex Men/Women n (%)	Age < 65 y / ≥ 65 y n (%)	Ethnicity White/Blk/Latino/Other n (%)
Placebo	17 (27)/ 46 (73)	53 (84) / 10 (16)	45 (71)/ 6(10)/ 8(13)/ 4(6)
Anakinra	17 (27)/ 46 (73)	48 (76) / 15 (24)	52 (83)/ 8(13)/ 1(2)/ 2 (3)

Diagnosis and Main Criteria for Eligibility: Adults between 18 and 74 years of age who had a diagnosis of rheumatoid arthritis at least 12 weeks before entering the study and who had not received a tetanus vaccine within 10 years.

Investigational Product, Dose and Mode of Administration: The investigational product was supplied in single-use 1-mL prefilled glass syringes with 27-gauge needles containing 140 mM sodium chloride, 10 mM sodium citrate, 0.1% (w/w) polysorbate 80, 0.5 mM edetate disodium, and was administered as daily SC 100 mg injections either by the subject or a caregiver.

Duration of Treatment: 8 weeks, with follow up at 10 weeks

Efficacy Endpoints:
Primary Endpoint: Proportion of subjects that achieve an anti-tetanus antibody response at study week 8 (4 weeks after injection of the vaccine), based on at least a 4-fold increase in antibody titers relative to week 4 (prevaccination).
Secondary Efficacy Endpoints: Anti-tetanus antibody titers at weeks 4 and 8; anti-tetanus antibody concentration changes from baseline to week 4, and from week 4 to week 8; and proportion of subjects with antibody levels ≥ 0.1 IU/mL at week 8.
Safety Endpoints: Assessments of deaths, serious and severe adverse events, all adverse events, and discontinuations due to adverse events and infections. The other safety endpoint was the assessment of laboratory data.

Statistical Methods:
Efficacy – primary endpoints: A 2o-sided 95% confidence interval was constructed for the difference between treatment groups in the percent of subjects achieving a positive anti-tetanus antibody response at week 8 (≥ 4-fold increase from week 4 to week 8). All randomized subjects who received investigational product and the vaccine were included in the analysis.
Efficacy – secondary endpoints: Analysis of covariance (ANCOVA), geometric mean antibody titers, and 95 percent confidence intervals.
Safety: For subjects who received at least one dose of investigational product, the subject incidence rates of treatment-emergent adverse events in each treatment group were tabulated by body system, preferred term, and severity. Laboratory values were summarized for weeks 4 and 8 and compared with baseline values; for continuous variables, summary statistics are presented as number, mean, standard deviation, median, minimum, and maximum; categorical variables are presented as shift tables.

Summary
Subject Disposition Results: The protocol-specified sample size was 144 subjects, 72 subjects per treatment arm. Of 148 subjects screened for enrollment, 126 were randomly assigned: 63 to the anakinra group and 63 to the placebo group. Premature discontinuation occurred in 19% of subjects in the anakinra group and 13% in the placebo group. The study was slow to enroll, and it was subsequently decided to

complete the study with fewer subjects than originally planned.
Efficacy Results: The primary endpoint was the proportion of subjects who achieved a positive anti-tetanus antibody response 4 weeks after tetanus/diphtheria vaccination, ie, an increase of at least 4-fold from week 4 to week 8. Primary response data were also stratified by methotrexate use vs no use of methotrexate. Overall responses in the two groups were similar, ie, 66% of subjects in each group had a positive antibody response. Methotrexate administration did not appear to have a clinically meaningful effect on the primary endpoint response.
Anakinra did not differ significantly from placebo in results of the secondary endpoints. When either univariate or multivariate logistic regression models were fitted to the anti-tetanus antibody response at week 8, none of the prespecified covariates associated with odds ratio estimates of relative risk were significant at the 5% level (alpha = 0.05).
Results of Anti-anakinra Antibody Testing: Only 3 of 62 subjects receiving anakinra (4.8%) and none of the 62 subjects receiving placebo (0.0%) developed neutralizing antibodies to IL1Ra in the study. The presence of neutralizing antibodies in patients treated with anakinra was not clinically relevant with respect to safety profile. No serious adverse events were observed in patients with neutralizing antibodies. In particular, no worsening or flares of rheumatoid arthritis or infections were observed. Injection site reactions, which are common with anakinra, were the only severe adverse events observed in these patients.
Safety Results: Anakinra was well tolerated, with no deaths or serious infections and 1 serious adverse event (deep venous thrombosis, anakinra group). Approximately three-quarters of anakinra subjects, 47 (75.8%), reported 1 or more adverse events compared with approximately half, 30 (48.4%), of all evaluable placebo subjects. However, only four of 62 (6.5%) anakinra subjects reported severe adverse events: none was life threatening. Events related to the site of injection were the most prevalent: 41 (66.1%) anakinra group subjects and 12 (19.4%) placebo group subjects. The next most common category was infections with subject incident rates of 11 (17.7%) of anakinra subjects and 8 (12.9%) of placebo subjects; the most common infection was urinary tract infection (4 [6.5%] subjects in the anakinra group and 2 [3.2%] subjects in the placebo group).

Conclusions: Anakinra was well tolerated in subjects receiving anti-tetanus vaccination, with a safety profile consistent with that seen in previous anakinra studies. No difference was detected in anti-tetanus antibody response between the anakinra and placebo treatment groups after receipt of an anti-tetanus vaccine. The most frequently reported adverse events were related to the site of injection. No serious or severe adverse events were observed in subjects with anti-anakinra neutralizing antibodies. In particular, no worsening or flares of rheumatoid arthritis or infections were observed in those subjects.