

1. TITLE PAGE

Study Title:	Open-label, Long-term Extension Study of Etanercept in the Treatment of Patients With Ankylosing Spondylitis who Participated in Protocol 016.0037
Investigational Product:	Recombinant human TNFR:Fc (etanercept)
Indication:	Ankylosing spondylitis (AS)
Brief Description:	In this phase 3, multicenter study, subjects received 50 mg etanercept, initially given 25 mg twice weekly and later, by amendment, once weekly as two 25-mg subcutaneous injections; therapy duration was up to 168 weeks. Endpoints included clinical efficacy, safety, physical function, and radiographic disease progression.
Study Sponsor:	Immunex Corp, a wholly-owned subsidiary of Amgen Inc, Thousand Oaks, CA US
Study No.:	016.0040 (Amgen Study 20021640)
IND No.:	BB-IND 10043
Study Phase:	3
Study Initiation Date:	21 May 2002 (first subject enrolled)
Study Completion Date:	15 February 2006 (last subject visit)
Clinical Study Manager:	Theresa Robertson, RN, MSN Phone: 805-447-0692
Good Clinical Practice:	This study was conducted in accordance with the principles of Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	13 August 2007 Previous: 016.0040 2-year Report dated 10 March 2006

2. SYNOPSIS

Name of Sponsor: Immunex Corp, wholly-owned subsidiary of Amgen Inc, Thousand Oaks, California USA

Name of Finished Product: Etanercept

Name of Active Ingredient: Recombinant human tumor necrosis factor receptor (rHuTNFR:Fc)

Title of Study: Open-label, Long-term Extension Study of Etanercept in the Treatment of Patients With Ankylosing Spondylitis who Participated in Protocol 016.0037

Publications: Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor α receptor fusion protein etanercept. *Arthritis Rheum.* 2005;4:1216-1223.

Boonen A, Patel V, Traina S, Chiou C, Maetzel A, Tsuji W. Rapid and sustained improvement in health-related quality of life and utility over 2 years in patients with ankylosing spondylitis receiving etanercept. *J Rheum.* In press.

Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept for ankylosing spondylitis for up to two years. *Ann Rheu Dis.* 2005; 64: 1557-1562.

Study Period: 21 May 2002 (first subject enrolled) to 15 February 2006 (last subject visit)

Development Phase: 3

Introduction and Objectives: Data from the preceding phase 3 double-blind, placebo-controlled study (016.0037) showed that etanercept was efficacious and well tolerated when administered to subjects with active AS for 24 weeks. This phase 3, follow-up, open-label study (016.0040 [Amgen Study 20021640]) was designed to monitor extended safety and efficacy of etanercept and to supplement the preceding study.

The objectives of this study were:

- To evaluate extended safety of etanercept (50 mg, weekly) in subjects previously enrolled in Protocol 016.0037.
- To evaluate efficacy of etanercept in subjects previously treated with placebo in Protocol 016.0037 and durability of benefit in all subjects.
- To determine the effect of etanercept in adults with AS on quality of life, employment status, and health resource utilization.
- To determine radiographic progression in patients with AS treated with etanercept for up to 4 years compared to a historic population (OASIS) that has not been treated with anti-TNF agents.
- To compare radiographic damage in subjects with AS treated with etanercept for up to 4 years to their radiographic damage at baseline and at time when treated with etanercept for up to 2 years.
- To compare the change in radiographic damage in subjects with AS from baseline to up to 2 years of etanercept treatment with their change from up to 2 years of etanercept treatment to up to 4 years of etanercept treatment.

Methodology: This study was designed to have an initial 4-week screening period, a 168-week open-label treatment period, and a 30-day follow-up period. All eligible subjects were to receive 50 mg etanercept, initially given 25 mg twice weekly and later, by amendment, once weekly as two 25 mg subcutaneous (SC) injections. Efficacy and safety evaluations were to be performed at baseline, and at 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 144, and 168 weeks. Patient-reported outcomes (Medical Outcomes Study Short Form Health Survey-36 [SF-36] and EuroQol [EQ-5D]) were to be assessed every 3 months until week 120 and components of the American College of Rheumatology criteria were assessed every 3 months until week 168. Radiographs were taken at baseline of Study 016.0037, and at weeks 72 and 168 of Study 016.0040.

Number of Subjects Planned: 250

Number of Subjects Enrolled: 257 (129 [placebo] 128 [etanercept] in Study 016.0037)

Sex: 75% men

Mean (SD) Age: 41.6 (10.2) years, range 18 to 70 years

Ethnicity (Race): 93% White; 4% Hispanic; 2% Asian; 1% Native American; < 1% Other

Diagnosis and Main Criteria for Eligibility: Eligible subjects who had completed 24 weeks of investigational product (placebo or etanercept) in Study 016.0037 were permitted to enroll directly into the present follow-up open-label Study (016.0040). Previous treatment with anti-TNF agents, other than in Study 016.0037, was not permitted.

Duration of Treatment: Maximum of 168 weeks

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was used for this open-label study.

Study Endpoints

Clinical Efficacy Endpoints: The primary efficacy endpoint for this study was the Assessment in Ankylosing Spondylitis (ASAS) International Working Group response criteria at the 20% level (ASAS 20). Additional efficacy endpoints included measures of spinal mobility, complete joint assessment, laboratory assessment of inflammation with C-reactive protein, and ability to reduce and discontinue specific concomitant medications.

Radiographic Endpoints: The primary 2-year radiographic endpoint was the change in modified Stoke Ankylosing spondylitis Spine Score (mSASSS [spine x-ray score]) from baseline to 2 years. The primary 4-year radiographic endpoint was the change in spine radiographic score (mSASSS) from baseline to 2 years compared to the change in mSASSS from 2 years to 4 years. Additional endpoints were the results of dual x-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) scans and radiographs of the cervical and lumbosacral spine.

Safety Endpoints: Safety endpoints included physical exam, vital signs, hematology and chemistry profiles, urinalysis, anti-etanercept antibodies, premature discontinuation, and adverse events.

Statistical Methods: For continuous variables, summary statistics include the number of observations, mean, standard deviation, median, minimum, and maximum were provided. For categorical data, the frequency and percent of subjects were provided.

The percentage of ASAS 20 responders was determined over time by original treatment group in Study 016.0037. Data from Study 016.0040 were combined with data from Study 016.0037 to assess the durability of the ASAS response rates over the duration of the 2 studies. Similar

analyses were conducted for the ASAS response at the 50% and 70% levels. Physical component score (PCS) and mental component score (MCS) for the SF-36 as well as the EQ-5D scores were compared over time by original treatment group. Statistical significance was tested using 2 sample t-test. For radiographic endpoints, summary statistics were provided. The 2-year primary radiographic endpoint compared the etanercept group to the Outcome in Ankylosing Spondylitis International Study (OASIS) group at the 2-sided 0.05 significance level using the Quade rank analysis of covariance, adjusted for baseline-mSASSS. For the 4-year radiographic endpoints, Wilcoxon signed rank test at the 2-sided 0.05 significance level was used to compare the change of mSASSS from 2 years of etanercept treatment to 4 years to the change from baseline to 2 years. Safety endpoints were compared descriptively. Post-hoc data for quality adjusted life-year (QALY) were not tabulated for this report. However, QALY data and analysis were submitted for publication and are included in this report (A Boonen, unpublished data, June 2007 [manuscript on file]).

Summary of Results

Subject Disposition: All of the 257 subjects (129 [placebo] 128 [etanercept] in Study 016.0037) who enrolled in Study 016.0040 received ≥ 1 dose of etanercept and were analyzed for safety and efficacy; 126 of these subjects (49.0%) completed all 168 weeks of the study. One hundred and thirty-one subjects (51.0%) withdrew before completing the study; the most common reasons for withdrawal ($> 5\%$) were patient refusal (10.1%); adverse event, infection, or injection-site reaction (8.2%); and lack of efficacy (7.8%).

Efficacy Results: After 168 weeks of open-label etanercept treatment, etanercept continued to provide clinically meaningful results in subjects with AS, as shown by ASAS 20, ASAS 50, and ASAS 70 responses that were maintained or improved in subjects who received etanercept therapy during this open-label study regardless of treatment group in the preceding placebo-controlled double-blind study (016.0037); these results were analyzed using the available cases analysis. By week 12 of open-label Study 016.0040, 69% of subjects who initially received etanercept and 72% of subjects who were previously randomized to placebo in Study 016.0037 had achieved an ASAS 20 response; by week 168, 81% and 82% subjects, respectively, had achieved this endpoint. A similar pattern was noted in the more stringent measures of ASAS 50 (56% [etanercept] and 49% [placebo in Study 016.0037] by week 12; 70% and 62%, respectively, by week 168) and ASAS 70 (36% [etanercept] and 28% [placebo in Study 016.0037] by week 12; 59% and 40%, respectively, by week 168).

Radiographic Results: The radiographic data for the primary 2-year analysis showed that there was no statistically significant difference between the etanercept and OASIS population for the change in mSASSS ($p = 0.996$) using the neighborhood imputation. The radiographic data for the primary 4-year analysis suggest that AS disease progression continued in subjects who received etanercept continuously throughout the study, however, disease progression after long-term treatment with etanercept (from 2 to 4 years) seemed to be slower than after short-term treatment with etanercept (from baseline to 2 years); this difference was on the border of statistical significance ($p = 0.0536$).

Patient-reported Outcomes: Subjects who received placebo in Study 016.0037 showed improvement in patient-reported outcomes including SF-36 and EQ-5D with etanercept treatment by week 12 of Study 016.0040. Improvement in patient-reported outcomes were sustained over time in both the previous placebo and etanercept groups.

The average 72-week QALY gain per person for subjects who previously received placebo was 0.24 and 0.10 for EQ-5D and SF-6D, respectively.

Safety Results: Etanercept was generally well tolerated during this open-label study. No deaths were reported. A total of 15.1% of subjects reported either serious adverse events (12.8%) or serious infectious events (2.3%) during the study; the most common serious adverse events and serious infectious events reported by 2 or more subjects were depression (1.2%), back pain

(0.8%), cellulitis (0.8%), fatty liver (0.8%), and malnutrition (0.8%). The most common adverse events (> 15%) were headache (20.2%); diarrhea (17.5%), and accidental injury (16.0%).

Antibody Results: A total of 242 of 257 subjects (94.2%) who had ≥ 1 pre-dose and post-dose sample were analyzed for anti-etanercept antibodies. Only 1 subject developed non-neutralizing anti-etanercept antibodies at a single time point (the end-of-treatment visit [week 168]). No subjects tested positive for neutralizing anti-etanercept antibodies.