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1401 Rockville Pike
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Memorandum

Division of Clinical Trial Design and Analysis
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Advisory Committee Meeting
Clinical Review Briefing Document

STN 103795 / 5123

Etanercept for the Treatment of Ankylosing Spondylitis

Applicant: Immunex, Inc.

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Introduction

The purpose of this meeting is to present to the Arthritis Advisory Committee data submitted in support of a claim for the use of ENBREL® (Etanercept) for the treatment of adult patients with Ankylosing Spondylitis (AS) and to discuss issues related to the measurement of clinical efficacy in this disorder.

Filing of Application

On January 23, 2003, Immunex Corporation submitted to FDA a License Application for Enbrel®(Etanercept) to extend the Indication to treatment of patients with active Ankylosing Spondylitis

Study Products

Etanercept 25 mg administered subcutaneously(SC) twice per week supplied to the pharmacies as a sterile lyophilized powder in vials containing 25 mg of etanercept, 40mg mannitol USP, 10mg sucrose, NF and 1.2 mg TRIS USP
Placebo also administered SC twice per week was supplied in vials identical to above but without the etanercept.

Ankylosing Spondylitis and its Treatment

Ankylosing spondylitis is a chronic inflammatory rheumatic disease of unknown etiology associated with HLA-B27. It affects primarily the sacroiliac joints and the axial skeleton, although peripheral joint involvement may also be an important feature. Common clinical manifestations include lower back pain and stiffness, chest pain, extra-articular tenderness due to enthesitis (an inflammatory reaction at the site of insertion of tendon into bone) and joint pain and effusion. Extraskeletal manifestations are seen in some patients, including uveitis, aortic incompetence, cardiac conduction abnormalities and lung fibrosis. Ankylosing spondylitis belongs to a group of rheumatic disorders, termed spondylarthropathies, that also includes Reiter's syndrome/reactive arthritis, the arthropathy of inflammatory bowel disease, psoriatic arthritis and undifferentiated spondyloarthropathies. Symptoms of ankylosing spondylitis are usually manifest by late adolescence or early adulthood. The course of disease is highly variable. While it is often self-limited, it may remain active over many years. Work disability has been observed in up to 15% of patients after 10 years of disease and in up to 45% of patients after 20 years of disease (Guillemin F, Briancon S et al. Arthritis Rheum 33:1001, 1990). While medications have not been demonstrated to reduce the rate of disability, a number of other interventions have been hypothesized to affect the progression of disability, including physiotherapy, vocational counseling and job training.

Approximately 350,000 patients in the United States have been diagnosed with AS. A variety of non-steroidal anti-inflammatory drugs (NSAIDS) are approved for treatment of signs and symptoms of AS. Certain drugs which are considered disease-modifying drugs (DMARDS) in rheumatoid arthritis (RA) such as Sulfasalazine or Methotrexate are used by some clinicians in AS but none are FDA approved for this use There are no data from randomized controlled clinical trials to support clinical benefit for DMARDS in AS.

Tumor necrosis factor (TNF) levels have been shown to be elevated in serum and synovial tissue of patients with AS. These findings provide a rationale for the study of the TNF blocking agent etanercept to reduce the clinical signs and symptoms of AS.

Etanercept has been approved for the treatment of Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis and Psoriatic Arthritis based upon randomized controlled trials that have shown safety and efficacy. Since AS may share pathogenic mechanisms with these disorders, efficacy for etanercept in these other disorders supports the rationale to study etanercept in AS.

Development of Efficacy Endpoints for Clinical Trials

Derivation of the ASAS Response Criteria

One of the difficulties encountered by investigators seeking to demonstrate benefit of various therapeutic modalities has been the lack of a outcome assessment similar to the ACR 20 used in Rheumatoid Arthritis to assess short-term benefit of therapies in this chronic disease. Over the years a number of questionnaire based instruments have been developed including the Bath Ankylosing Spondylitis Functional Index (BASFI) which measures the physical function impairment caused by AS, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) which focuses upon signs and symptoms of the inflammatory aspects of AS, nocturnal and total back pain, the patient's global assessment and actual physical measurements of spinal mobility such as the Schober's test, chest expansion score and Occiput to wall measurement. The Assessments in Ankylosing Spondylitis (ASAS) Working Group developed and published a core set of 5 domains whose evaluation were deemed essential in the evaluation of the therapeutic efficacy. These domains were: physical function, pain, spinal mobility, spinal stiffness/inflammation and patient's global assessment. In 2001, the ASAS Working Group published the ASAS Response Criteria based upon analysis of 5 randomized trials of NSAIDS in AS which enrolled 1030 patients for ≤ 6 weeks of treatment. Four of the five necessary domains were included in the Response Criteria since in these placebo response rates were low and using these response criteria effectively differentiated drug effect from placebo. The remaining domain, spinal mobility was omitted from the Response Criteria because of a lack of responsiveness possibly owing to the lack of effect of NSAIDS on spinal mobility as well as the short duration of treatment.

The ASAS Working Group Response Criteria were used in both Phase 3 studies in this application, and were compared with pre-specified response criteria used in the phase 2 study.

Clinical Studies of Etanercept for Ankylosing Spondylitis

The studies of etanercept in AS are summarized in (**Table 1**)

Table 1 Clinical Studies of Etanercept 25mg biw for Ankylosing Spondylitis

Protocol No. Study Objectives	Treatment Duration N	Treatment Groups
016.0026 Phase 2 Efficacy and safety	16 weeks 20	Etanercept 25mg sc biw
	16 weeks 20	Placebo sc biw
016.0037 Phase 3 Efficacy, safety, PK	24 weeks 138	Etanercept 25mg sc biw
	24 weeks 139	Placebo sc biw
47687 Phase 3 Efficacy and safety	12 weeks 45	Etanercept 25mg sc biw
	12 weeks 39	Placebo sc biw

Including patients participating in the phase 2 study and the two phase 3 studies to be discussed, a total of 203 patients with active Ankylosing Spondylitis have received etanercept at 25mg sc biw for a duration of between 12 and 24 weeks during the conduct of this clinical development (**Table** 1).

Etanercept (Enbrel) is a dimeric fusion protein consisting of the human p75 tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG1. It binds specifically to TNF and blocks its interaction with cell surface TNF receptors. It is approved for treatment of moderately to severely active rheumatoid arthritis and for treatment of active arthritis in patients with psoriatic arthritis. Etanercept is approved as monotherapy or in combination with methotrexate for patients who do not respond adequately to methotrexate alone. It has been shown to reduce signs and symptoms in rheumatoid arthritis and to inhibit the progression of structural damage. It is also approved for treatment of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs.

The safety of etanercept has been studied in clinical trials of approximately 1200 patients with RA, followed for up to 36 months and in 157 patients with psoriatic arthritis for 6 months. In addition, over 100,000 patients have been exposed to the marketed product. Serious adverse events are observed infrequently with etanercept and include serious infections and sepsis, demyelinating syndromes and lupus-like syndrome. A recent FDA analysis of the clinical trial data with etanercept, infliximab and adalimumab suggested that use of TNF-blocking agents may be associated with a higher risk of lymphoma. For etanercept, the rate of lymphoma was 2-fold higher than that expected in the general population. However, patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk for the development of lymphoma.

Summary of Phase 2 Study

The phase 2 Study 160026 was a randomized, double-blind, placebo controlled trial designed to explore the clinical efficacy of etanercept in controlling disease activity of AS in conjunction with the use of standard medication for AS. Eligible patients were randomized 1:1 to receive either etanercept 25 mg biw or placebo biw. Duration of the trial was 16 weeks with 4 weeks of safety follow-up. This trial commenced in 1999 prior to the publishing of the ASAS Working Group Response Criteria and utilizes a somewhat different set of Clinical Response Criteria that comprised the Bath Ankylosing Spondylitis Functional Index (BASFI), Nocturnal Back Pain Visual Analogue Scale (VAS), Patient Global Assessment VAS, Duration of Morning Stiffness and Swollen Joint Score. Analysis using the pre-specified endpoint indicated increased response rate associated with etanercept treatment. In addition, an ad hoc analysis using the ASAS Working Group Response Criteria was performed and it also showed increase in response incidence with etanercept treatment. This study will be reviewed further later in this document

Rationale for Selection of Etanercept Dosage for Phase 3

Etanercept at a dose of 25 mg administered SC twice weekly was selected for this study based on clinical trials in patients with RA and psoriatic arthritis, which have shown this to be an effective dose, and because this dose appeared to provide benefit in the earlier Phase 2 trial in patients with AS

Summary of Study 016.0037

Study Title

" Multicenter, double-blind, Placebo-controlled, Randomized Phase 3 Study of Etanercept (ENBREL®) in the Treatment of Patients with Ankylosing Spondylitis"

Study Design

Study 016.0037 was a randomized, multicenter, international, double blinded, placebo-controlled phase 3 study of etanercept versus placebo in 277 patients with active ankylosing spondylitis. Subjects were randomly assigned to one of two treatment arms: etanercept 25mg sc biw or placebo on a 1:1 basis. Subjects were treated for a total of 24 weeks with the primary efficacy endpoint determined at week 12 and a conditional primary efficacy endpoint determined at week 24 if efficacy was demonstrated at week 12. There were 4 weeks of safety follow-up after the 24 weeks of study treatment. Randomization was stratified for the presence of DMARDS approved for use in the study. These were Sulfasalazine, Methotrexate and Hydroxychloroquine.

Dosing and Dosing Modification

Etanercept 25 mg or placebo was administered sc twice per week for 24 weeks in patients with active AS who met eligibility criteria. There was no provision for dose modification of study drug. Patients who developed a Grade 3 or 4 adverse event thought to be related to study treatment could suspend study drug for one week but if 4 consecutive doses of study drug were missed, the subject was withdrawn from the study. In this situation, the subject was considered to be a treatment non-responder for efficacy and would continue for an additional 30 days for safety analysis.

Study Population
Men and women, outpatients, between 18 and 70 years of age with AS, as defined by the modified New York Criteria for Ankylosing Spondylitis (**Table 60 Appendix A**) which was active at the time of enrollment as defined by:

- visual analog scale (VAS) values ≥ 30 (on a scale of 0–100) for the following parameter:
- Average of duration and intensity of morning stiffness

PLUS VAS values ≥ 30 for 2 of the following 3 parameters:

- patient global assessment
- average of VAS values for nocturnal back pain and total back pain
- average of 10 questions on the BASFI.

Excluded were subjects with:

Complete Ankylosis of the spine
Use of DMARDS other than Sulfasalazine, Methotrexate, or Hydroxychloroquine
Previous Receipt of Etanercept or other TNFα-blocking agents
Dose of prednisone > 10mg/d or changed within 2 weeks of baseline evaluation
Dose of NSAIDS changed within 2 weeks of baseline

Primary Efficacy Outcome
The primary efficacy outcome was determined at 12 weeks of treatment using the following ASAS Response Criteria

- Primary Efficacy Endpoints:
  ASAS Response Criteria (ASAS 20) at 12 weeks defined as follows:
  - An improvement of at least 20% and absolute improvement of at least 10 units on a 0-100mm scale in at least 3 of the following domains:
    - Patient global assessment measured on a VAS scale with extremes labeled "none" and "severe." **(Table 65 Appendix F)**
    - Pain assessment represented by the average of total and nocturnal pain scores, both measured on a VAS scale with extremes labeled "no pain" and "most severe pain." **(Table 66 Appendix G)**
    - Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS with extremes labeled "easy" and "impossible." **(Table 62 Appendix C)**
    - Inflammation, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS: one (No. 5) with extremes labeled "none" and "very severe"; the other (No. 6) marking duration of morning stiffness between "0" and "2 or more hours." **(Table 63 Appendix D)**
  - Absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0–100 mm scale) in the remaining domain.

Secondary Efficacy Outcomes:
Secondary Efficacy Outcomes included:

- The ASAS Response Criteria of 50% and 70% improvement at weeks 12 and 24 which were calculated as follows:

- The ASAS 50 response was to be computed and analyzed using rules similar to those defined for the ASAS 20 response criteria, except that a 50% improvement was required for 3 of the 4 components, in addition to a ≥ 10 point absolute improvement in the change scores for 3 of the 4 components. The deterioration criteria were to be defined exactly as for the ASAS 20 response criteria (worsening of 20% or more and absolute worsening of ≥10 points).
- The ASAS 70 response was to be computed and analyzed using rules similar to those defined for the ASAS 50 response criteria, except that a 70% improvement was required.
-Additional analysis of ASAS response at Weeks 12 and 24:

- Highest ASAS Level Achieved

- Patients were to be classified on 1–4 scale according to their highest response status with respect to ASAS 20, ASAS 50, and ASAS 70 endpoints.
  - 1 = non-responder (did not achieve ASAS 20 response)
  - 2 = ASAS 20 responder, but not ASAS 50 responder
  - 3 = ASAS 50 responder, but not ASAS 70 responder
  - 4 = ASAS 70 responder

- Partial Remission

  Frequency and time to the ASAS definition of partial remission defined as:

  Value of < 20 (on a scale of 0–100) in each of the following 4 domains
  - Patient global assessment as determined by VAS.
  - Pain score (average of total back pain/nocturnal back pain) determined by VAS.
  - BASFI.
  - Average of responses to 2 questions regarding morning stiffness on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Additional Outcome Measures:
In addition to the primary and secondary endpoint analysis as listed above, additional outcome analysis was performed using both the individual components of the ASAS Response Criteria as well as Components of Other AS Instruments.

Individual components of the ASAS Instrument

- Patient global assessment
- Nocturnal back pain, total back pain, and the average of the nocturnal back pain and total back pain scores
- The BASFI and its independent components
- The BASDAI and its independent components

Components of Other AS Instruments

- Spinal mobility (change and percent change from baseline) assessed by:
  - modified Schober's test
  - chest expansion score
  - occiput-to-wall measurement.
- Peripheral tender joints and swollen joint count (change and percent change from baseline).
- Laboratory assessment of inflammation (CRP and ESR), change and percent change from baseline.
- Patient-reported improvement in AS at 2 weeks (percent of patients).

- Assessor global assessment (change and percent change from baseline).

Withdrawal for Lack of Efficacy
Patients could be discontinued from study treatment for lack of efficacy defined as failure to improve 3 of 4 ASAS Response Criteria by 10% or more at week 8 (and 12) and at early termination visit. Such an individual would be considered an efficacy non-responder and would continue for 30 days for safety analysis only.

Clinical and Laboratory Evaluations
Patients were assessed for both efficacy and safety at weeks 2,4,8,12, 24 (or Early Termination) and at 30-day follow-up. All components of the ASAS Response Criteria as well as Assessor global score and blinded joint assessment were performed at these times. Physical examination including vital signs as well as measurements of spinal mobility were performed at those visits. Laboratory evaluation including Chemistry profile, urinalysis were scheduled to be performed at baseline, week 12 and 24 and at 30 day follow-up. ESR and C-reactive Protein were to be performed with each efficacy/safety visit except for the 30 day follow-up. All Laboratory tests except ESR were performed centrally and all results were withheld from the investigator until after the study was un-blinded.

Statistical Analyses

Primary efficacy analysis

- The primary efficacy population was the modified Intention to Treat population which was defined as all subjects randomized and who received at least one dose of study medication. The acceptance of the modified Intention to Treat population was contingent upon the number of randomized but not treated being small and balanced between the two arms. Otherwise, the primary analysis population would be the strict intend to treat population, i.e. all randomized patients.
- The ASAS 20 response rates were to be compared between the etanercept and placebo groups at each time point using the Cochran-Mantel-Haenszel test stratified by presence or absence of concomitant DMARDS at baseline.

Secondary analyses:

- For binary endpoints (ASAS 50 and ASAS 70 response rates, partial remission of AS, and patient improvement at 2 weeks), the Cochran-Mantel-Haenszel row means test, stratified by presence or absence of concomitant DMARDs at baseline, was to be used to compare the etanercept and placebo treatment groups at each time point.
- For patient and assessor global assessment, back pain, BASFI, BASDAI, chest expansion score, modified Schober's test, occiput-to-wall measurement, numbers of tender and swollen joints, and acute phase reactants, change and percent change from baseline were to be compared between the etanercept and placebo groups at each time point using a stratified rank test as obtained in PROC FREQ from SAS using Modridit scores. The p-value obtained from the row-means test statistic was to be used. Change and percent change from baseline were computed for each variable such that a value greater than zero reflects improvement.

Values were measured at the patient level and then summarized. Patients with a score of zero at baseline were not included in the analysis of percent change for the variable in question. The scores for the highest response status (scale of 1– 4) with respect to ASAS 20%, 50%, and 70% responses were to be compared between the etanercept and placebo groups at each time point using the exact Kolmogorov-Smirnov test as given by PROC NPAR1WAY in SAS based on 500,000 Monte Carlo simulations. The time to first partial remission was to be analyzed using the log-rank test to compare between the etanercept and placebo groups.
All tests were 2-sided, conducted at the $\alpha = 0.05$ level.
Patients who prematurely discontinued from study drug were considered non-responders for all binary endpoints at time points after study drug discontinuation.

Major Protocol Amendments

Amendment 1: submitted approximately 6 weeks after the original protocol was approved this protocol increased the number of participating centers to 30 from 25 to insure rapid accrual, provided for a conditional primary endpoint defined by ASAS Response Criteria at Week 24 to be assessed if efficacy is established at Week 12, established that inclusion criteria were to be applied prior to randomization rather than enrollment, provided for Lack of Efficacy withdrawal at weeks 8, 12 and early termination visit rather than just after 12 weeks of treatment.
There were no additional protocol amendments

Study Results

Study Centers
There were 28 participating study centers in US, Europe, and Canada. The majority of the subjects participated at North American Sites (78%)

Patient Disposition
330 patients were screened, 284 were randomized and 277 were randomized and received at least one dose of the study medication. Of the 46 individuals screened but not randomized, 40 were found to be ineligible, the remainder declined participation. Of the 7 individuals who were randomized but did not receive study medication, 4 had been randomized in error (did not meet inclusion criteria) and 3 withdrew consent prior to first dose. These 7 individuals were equally balanced across both study arms. Of the 277 individuals that were randomized and received study medication, 138 received etanercept and 139 received placebo. 96% of all participants completed 12 weeks of study, and 86% of placebo and 91% of etanercept recipients completed 24 weeks of participation. Adverse Events were the most common reason for withdrawal in the etanercept group (7 patients or 5%) and Lack of Efficacy most common reason in the placebo group (13 patients or 9%) (Table 2)

Table 2: Study Completion Status at 12 and 24 Weeks

	Placebo (N = 139)	Etanercept (N = 138)
Patient Status	**n (%)**	**n (%)**
Randomized but not dosed	**3/142 (2)**	**4/142 (3)**
Completed 12 weeks in study	**134 (96)**	**132 (96)**
Discontinued study (wks 0-12) due to:		
Adverse event	**0**	**4 (3)**
Lack of efficacy (LOE)	**2 (1)**	**1 (1)**
Lost to follow-up	**0**	**1 (1)**
Patient refusal	**2 (1)**	**0**
Physician decision	**1 (1)**	**0**
Completed 24 weeks in study	**120 (86)**	**126 (91)**
Discontinued study (wks 0-24) due to:		
Adverse event	**1 (1)**	**7 (5)**
Lack of efficacy (LOE)	**13 (9)**	**3 (2)**
Lost to follow-up	**1 (1)**	**2 (1)**
Patient refusal	**2 (1)**	**0**
Physician decision	**2 (1)**	**0**

Patient Demographics

The mean age of study participants was approximately 42 years of age in both study arms. The study excluded pediatric patients and there was an upper age limit of 70 years of age. The mean weight of participants was approximately 82 kg in both arms with the recorded range from 47 kg and 165 kg. Etanercept was administered as fixed doses.

76% of the participants were male which reflects the higher prevalence of AS in men. More than 91% of participants were Caucasian, minority participation was low in both arms with only one subject identified as black in either arm (Table 3).

Table 3 Demographics 016.0037

	Placebo	Etanercept
Characteristic	**N = 139**	**N = 138**
Mean age in years	**41.9**	**42.1**
Male (n [%])	**105 (76)**	**105 (76)**
Race (n [%]):		
Caucasian	**127 (91)**	**130 (94)**
Hispanic	**6 (4)**	**3 (2)**
Asian	**3 (2)**	**3 (2)**
Native American	**3 (2)**	**0**
Black	**0**	**1 (1)**
Other	**0**	**1 (1)**
Mean weight (kg)	**83.1**	**82.2**

Disease Characteristics at Baseline

Axial Disease Characteristics

The mean duration of ankylosing spondylitis was similar in both arms at approximately 10 years. The percentage of HLA B-27 antigen positivity was identical at 84% in both arms and reflects the prevalence in the general patient population. Baseline assessment using the ASAS components indicated that the subjects had moderate mean values of disease activity and were well balanced between study arms. Approximately 92% of subjects had a history of NSAIDS usage, 13% had history of prior corticosteroid usage and 41% had received prior DMARDS. Approximately 32% of individuals in both arms were on protocol permissible DMARDS at baseline; the most common DMARD in both arms was Sulfasalazine (**Table 4**). Approximately 14% of placebo recipients and 12% of etanercept recipients received corticosteroids during the study, the most common reason for corticosteroid use was flare of pre-existent ocular inflammatory conditions.

Table 4 Baseline Disease Characteristics

	Placebo	Etanercept
Characteristic	**N = 139**	**N = 138**
Mean duration of AS in years	**11**	**10**
HLA B-27	**109(84)**	**108(84)**
Mean baseline ASAS components (range):		
Patient global assessment	**63(9–100)**	**63(16–100)**
Nocturnal and total back pain	**62 (0–99)**	**60 (6–100)**
BASFI	**56 (12–97.0)**	**52 (4–98)**
Inflammation	**64 (7–100)**	**61. (17–100)**
Concomitant therapy at baseline (n [%]		
Any DMARD	**43 (31)**	**44 (32)**
Sulfasalazine (SSZ)	**30 (22)**	**29 (21)**
Methotrexate (MTX)	**17 (12)**	**15 (11)**
Hydroxychloroquine (HCL)	**1 (1)**	**3 (2)**

Extra-Spinal Inflammatory Signs/Symptoms

Overall approximately 30% of participants had a history of or concurrent manifestations of extra-spinal inflammatory signs and symptoms. Ocular Inflammation or uveitis/iritis were the most common extra-spinal inflammatory conditions at approximately 30% in both arms. Patients with history of inflammatory bowel disease and psoriasis were included in the study and made up approximately 5% and 9% of the study population respectively (**Table 5**). These factors were well balanced between the two study arms.

Table 5 Extra-Spinal Inflammatory Symptoms

Extra-Spinal/Articular Inflammatory Symptom	Placebo n/N %	Etanercept n/N %
Occular Inflammation	**39/139 (28)**	**44/138 (32)**
Non-Infectious Conjunctivitis	**11/139 (8)**	**9/138 (7)**
Uveitis or Iritis	**43/139 (31)**	**39/138 (28)**
Crohns Disease or Ulcerative Colitis	**6/139 (4)**	**7/138 (5)**
Urethritis	**8/139 (6)**	**5/138 (4)**
STD	**13/139 (9)**	**11/138 (8)**
Psoriasis	**15/139 (11)**	**11/138 (8)**

Primary Efficacy Analysis

The primary efficacy endpoint in this study was the achievement of an ASAS 20 using the ASAS Working Group Response Criteria. 60% of Etanercept recipients versus 27% of placebo recipients achieved the primary endpoint which was statistically significant with a p-value of <0.0001 **(Table 6).**

Table 6 Primary Endpoint Study 016.0037

Primary Endpoint			
Number (%) Achieving ASAS 20 Response at Week 12			
	Placebo	**Etanercept**	
Parameter	**N = 139**	**N = 138**	**P-value***
ASAS 20 at 12 weeks	**38 (27)**	**83 (60)**	**< 0.0001**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Because the primary endpoint at 12 weeks was achieved, the ASAS Response Criteria data at 24 weeks was assessed as a conditional primary endpoint. In this analysis, ASAS 20 levels were achieved by 58% of Etanercept recipients versus 23% of Placebo recipients (p-value of <0.0001) **(Table 7).**

Table 7 Conditional Primary Endpoint Study 016.0037

Conditional Primary Endpoint:			
Number (%) Achieving ASAS 20 at Week 24			
	Placebo	**Etanercept**	
Parameter	**N = 139**	**N = 138**	**P-value***
ASAS 20 at 24 weeks	**32 (23)**	**80 (58)**	**< 0.0001**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Secondary Efficacy Analysis

There were 8 Secondary Efficacy Endpoints: Measurement of ASAS 50/70 at 12 and 24 weeks, Highest ASAS level achieved at 12 and 24 weeks and Frequency and time to Partial Remission as previously defined

ASAS 50/70 at 12 and 24 weeks

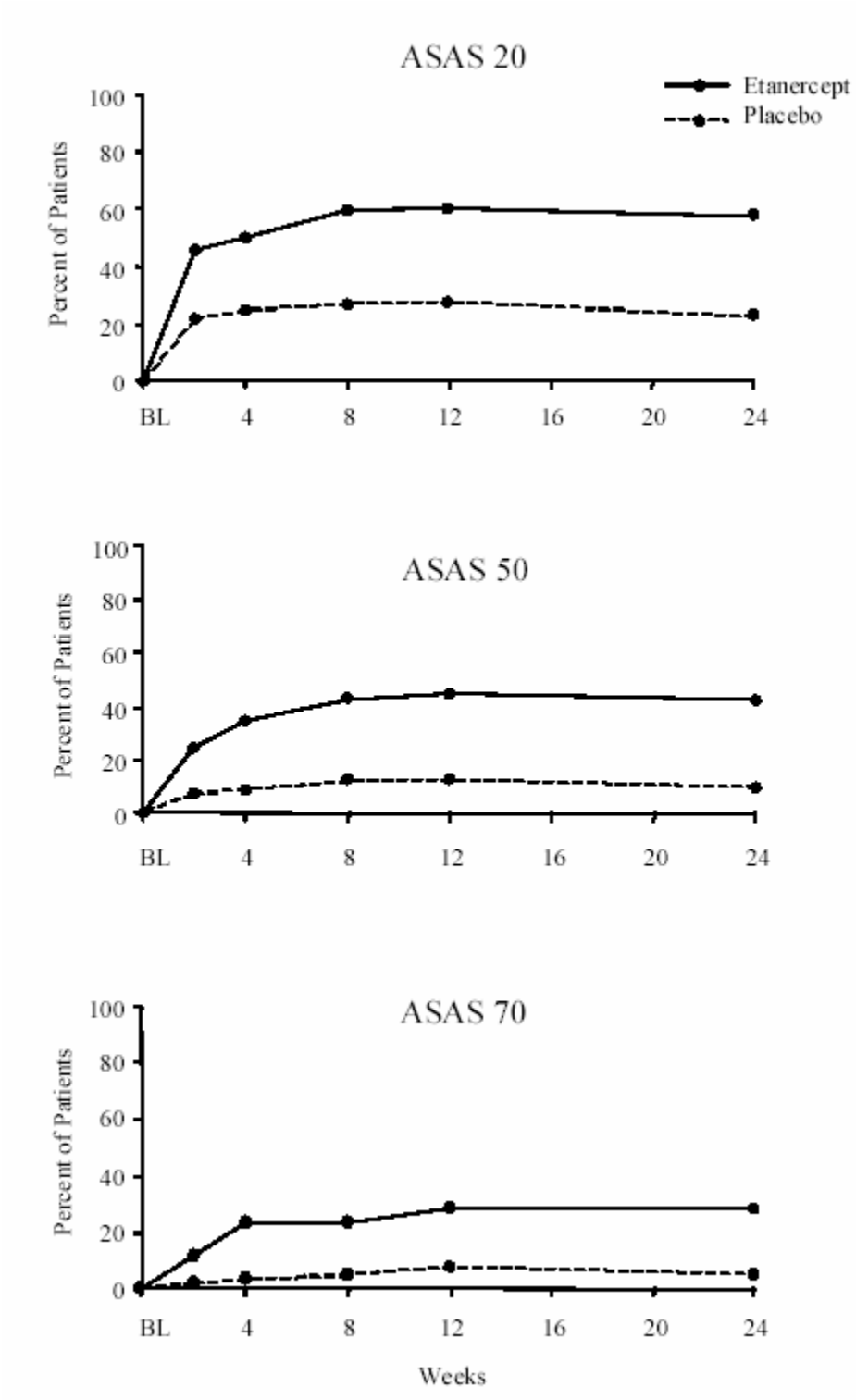
Higher levels of response using the ASAS Response Criteria were analyzed. The superior performance of etanercept compared to placebo was also seen in the ASAS 50 and 70 determinations with significant p-values at both 12 and 24 weeks (Table 8).

Table 8 Secondary Endpoints ASAS 20, 50, 70: 12/24 Weeks

Secondary Endpoints:			
	Placebo	**Etanercept**	
Parameter	**N = 139**	**N = 138**	**P-value***
ASAS 20 (n [%]) at:			
12 weeks	**38 (27)**	**83 (60)**	**< 0.0001**
24 weeks	**32 (23)**	**80 (58)**	**< 0.0001**
ASAS 50 (n [%]) at:			
12 weeks	**18 (13)**	**62 (45)**	**< 0.0001**
24 weeks	**14 (10)**	**58 (42)**	**< 0.0001**
ASAS 70 (n [%]) at:			
12 weeks	**10 (7)**	**40 (29)**	**< 0.0001**
24 weeks	**7 (5)**	**39 (28)**	**< 0.0001**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

The onset of etanercept treatment effect compared to placebo began to be apparent as early as 2 weeks after treatment initiation. Maximal treatment effect was reached at approximately 8 weeks and sustained thereafter **(see Figure 1).** The time courses of effect with respect to ASAS 20, 50, and 70 values were similar although smaller proportions of patients attained the higher levels of response criteria **(Figure 1**)

Figure 1: **Percent of Patients Achieving ASAS 20, ASAS 50, and ASAS 70 Over Time**



Highest ASAS Responses at weeks 12/24

Analysis of highest ASAS response achieved indicate that among the patients whose highest response was ASAS 20 (did not achieve an ASAS 50 or ASAS 70 response), the numbers and percentages are similar between the two study arms at the 12 and 24 week time points Higher proportions of etanercept treated patients achieved higher level (ASAS 50, 70) responses (Table 9).

Table 9 Secondary Endpoint Study: Highest ASAS Responses Achieved at weeks 12/24

	Secondary Endpoint: Highest ASAS 12/24 weeks			
		Placebo	**Etanercept**	
Time point	**Highest level of response**	**N = 139**	**N = 138**	**P-value***
Week 12	**ASAS 20 non-responder**	**101 (73)**	**55 (40)**	**< 0.0001**
	ASAS 20 responder	**20 (14)**	**21 (15)**	
	ASAS 50 responder	**8 (6)**	**22 (16)**	
	ASAS 70 responder	**10 (7)**	**40 (29)**	
Week 24	**ASAS 20 non-responder**	**107 (77)**	**58 (42)**	**< 0.0001**
	ASAS 20 responder	**18 (13)**	**22 (16)**	
	ASAS 50 responder	**7 (5)**	**19 (14)**	
	ASAS 70 responder	**7 (5)**	**39 (28)**	
* P-value determined by Kolmogorov-Smirnov test.				

Partial Remission

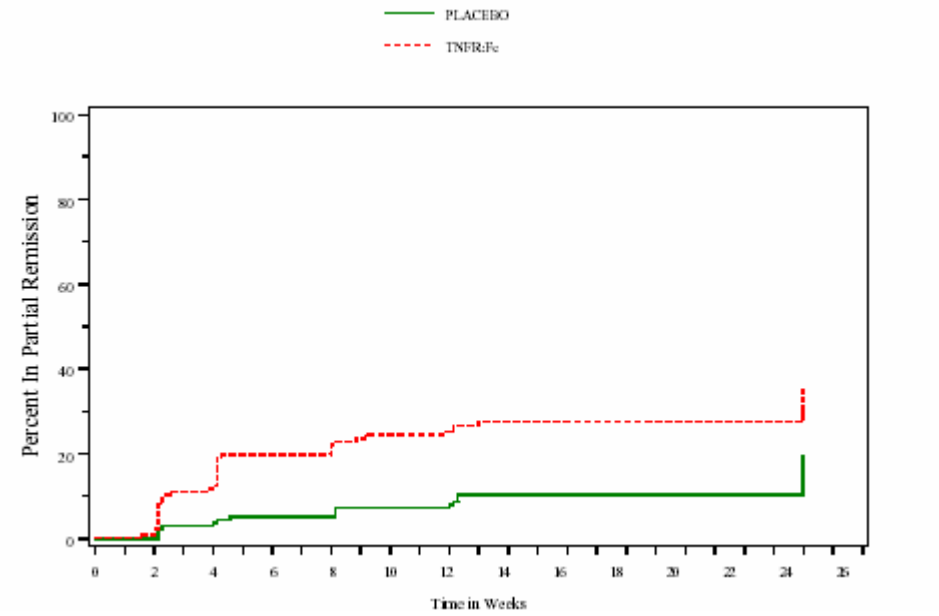
As previously indicated, partial remission was defined as achievement of a disease activity level <20 on VAS in all 4 ASAS domains. Etanercept patients achieved partial remission statistically more often than placebo both at the weeks 12/24 endpoints as well as any time during the study **(Table 10).**

Table 10 Secondary Endpoint Study Achievement of Partial Remission

Secondary Endpoint: Partial Remission			
	Placebo	**Etanercept**	
	N = 139	**N = 138**	
Time point	**n (%)**	**n (%)**	**P-value***
Week 12	**11 (8)**	**29 (21)**	**0.0020**
Week 24	**5 (4)**	**24 (17)**	**0.0002**
Any time during the study	**15 (11)**	**42 (30)**	**< 0.0001**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

The time to achievement of first partial remission was also analyzed and etanercept was statistically superior to placebo (log-rank p-value <0.0001) as shown graphically in **(Figure 2).**

Figure 2 Time to First Partial Remission



Other Efficacy Analysis

Individual Components of ASAS Response Criteria

Response data corresponding to each of the components of the 4 domains that comprise the ASAS Response Criteria were individually analyzed. The components analyzed using a Visual Analog Scale were: patient global assessment, average of nocturnal back pain and total back pain, the average of the 10 questions of the BASFI (function) and the last two questions of the BASDAI (inflammation). The results of this analysis indicated that subjects receiving etanercept had statistically greater improvement in each of the ASAS components than did subjects receiving placebo **(Table 11**).

Table 11 ASAS Individual Components

ASAS Individual Components					
Mean (median) Values and Percent Improvement from Baseline					
			Mean(median)		
	Mean (median) Values		**Percent Improvement from Baseline**		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Parameter	**N = 139**	**N = 138**	**N = 139**	**N = 138**	
Patient's Global Assessment	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	
Baseline	**63 (64)**	**63 (66)**			
12 weeks	**56 (57)**	**35 (32)**	**10 (9)**	**40.2 (51)**	**< 0.0001**
24 weeks	**56 (57)**	**36 (29)**	**8 (7)**	**38.6 (46)**	**< 0.0001**
Average of Nocturnal Back Pain/ Total Back Pain	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**62 (65)**	**60 (62)**			
12 weeks	**55 (56)**	**33 (26)**	**7 (5)**	**40 (54)**	**< 0.0001**
24 weeks	**56 (61)**	**34 (26)**	**5 (6)**	**35 (51)**	**< 0.0001**
BASFI	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**56 (59)**	**52 (50)**			
12 weeks	**53 (53)**	**35 (29)**	**5 (3)**	**33 (32)**	**< 0.0001**
24 weeks	**55 (55)**	**36 (31)**	**2 (1)**	**30 (31)**	**< 0.0001**
BASDAI (last 2 questions)	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**64 (65)**	**61.4 (60)**			
12 weeks	**53 (49)**	**32.8 (21)**	**13 (10)**	**45 (55)**	**< 0.0001**
24 weeks	**57 (58)**	**33.4 (26)**	**6 (5)**	**44 (45)**	**< 0.0001**

Additional Outcome Measurements

Efficacy measurements not part of the ASAS Response Criteria but which had been used in other studies of Ankylosing Spondylitis were also analyzed. These outcome measurements included: BASDAI (all 6 questions), spinal mobility parameters, peripheral tender and swollen joints, acute phase reactants and assessor global assessment.

BASDAI

The last 2 questions of the BASDAI deal with inflammation and are assessed in the ASAS response criteria. The other 4 questions address fatigue; AS related neck, back or hip pain; non-AS pain and swelling of joints and tenderness to touch of any areas. These data were collected and the results are presented in **(Table 12**). Again, the improvement in the etanercept group is statistically superior to the placebo.

Table 12 BASDAI Average of 6 questions

			Mean (median)		
	Mean (median) Values		Percent Improvement from Baseline		
BASDAI – average of responses to 6 questions	Placebo N = 139	Etanercept N = 138	Placebo N = 139	Etanercept N = 138	P-value*
Baseline	60 (60)	58 (57)			
12 weeks	52 (50)	33(27)	11 (10)	42 (45)	< 0.0001
24 weeks	55 (58)	35 (33)	6 (3)	40 (40)	< 0.0001
* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.					

Spinal Mobility Parameters

Spinal mobility was judged by the ASAS Working Group as the fifth important domain in the assessment of clinically important short-term therapeutic response in Ankylosing Spondylitis but this domain was not included in the ASAS Response Criteria (see Development of Efficacy Endpoints for Clinical Trials pg 3). Assessment of Spinal Mobility was separately performed in this study and these data are presented in **(Table 13**). Statistically significant improvements in spinal mobility in all three measured parameters were demonstrated by etanercept. The parameter demonstrating the greatest improvement was Occiput to wall measurement.

Table 13 Other Endpoints: Spinal Mobility Parameters

Spinal Mobility Parameters:					
Mean (median) Values and Percent Improvement from Baseline					
	Mean (median) Values (cm)		**Mean (median) Percent Improvement from Baseline***		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 139**	**N = 138**	**N = 139**	**N = 138**	**P-value†**
Modified Schober's test					
Baseline	**3.0 (3)**	**3.1 (3)**			
12 weeks	**3.1 (3)**	**3.3 (3)**	**21 (0)**	**26 (9)**	**0.0359**
24 weeks	**2.9 (3)**	**3.3 (4)**	**8 (0)**	**25 (10)**	**0.0014**
Chest expansion					
Baseline	**3.2 (3)**	**3.3 (3)**			
12 weeks	**3.2 (3)**	**3.8 (3)**	**11 (0)**	**58 (5)**	**0.0026**
24 weeks	**3.0 (3)**	**3.9(4)**	**-<1 (0)**	**57 (17)**	**< 0.0001**
Occiput-to-wall Measurement					
Baseline	**5.3 (3)**	**5.6 (5)**			
12 weeks	**5.7 (3)**	**4.9 (3)**	**-18 (0)**	**18 (16)**	**0.0034**
24 weeks	**6.0 (3)**	**4.5(1)**	**-18 (0)**	**26 (25)**	**< 0.0001**

* Patients with a score of zero at baseline were not included in the analysis of percent improvement from baseline.
The number of patients with a zero baseline score varied, depending on the parameter of interest.
† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Peripheral Tender and Swollen Joint Counts

Improvement in peripheral joint symptoms have been analyzed in other studies of Ankylosing Spondylitis and were assessed here. Treatment with etanercept was associated with statistically significant improvement in numbers of tender peripheral joints (**Table 14**). There was, however, no corresponding statistically significant improvement in the numbers of swollen joints **(Table 14**). The explanation for this finding is not established but is possibly related to the small number of involved joints symptoms in subjects in both study arms or to the lack of etanercept efficacy. At baseline, 82% of placebo recipients and 73% of etanercept recipients had at least one tender peripheral joint, 47% and 53% of these same groups had evidence of swelling in at least one peripheral joint. For those individuals who did have tender joints at baseline, the mean number was 9 in placebo and 7 in etanercept arms, with corresponding medians of 4 and 3 respectively. The mean number of swollen joints was 4 in both arms with corresponding medians of 0 for placebo and 1 for etanercept.

Table 14 Other Endpoints: Peripheral Tender and Swollen Joint Counts

Peripheral Tender and Swollen Joint Counts					
Mean (median) Values and Percent Improvement from Baseline					
	Mean (median) Values		**Mean (median) Percent Improvement from Baseline***		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 139**	**N = 138**	**N = 139**	**N = 138**	**P-value†**
Tender joints					
Baseline	**9 (4)**	**7 (3)**			
12 weeks	**8 (2)**	**5 (1)**	**-1.0 (21)**	**37 (50)**	**0.0061**
24 weeks	**8 (2)**	**5 (1)**	**1.4 (31)**	**36 (62)**	**0.0014**
Swollen joints					
Baseline	**4 (0)**	**4 (1)**			
12 weeks	**4 (0)**	**3 (0)**	**-15 (50)**	**36 (66)**	**0.1263**
24 weeks	**3 (0)**	**2 (0)**	**-11 (50)**	**4 (60)**	**0.8384**
* Patients with a count of zero at baseline were not included in the analysis of percent improvement from baseline. The number of patients with a zero baseline score varied, depending on the parameter of interest.					
† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.					

Acute Phase Reactants

At baseline the acute phase reactants, ESR and CRP were within the normal range in approximately 53% of placebo recipients and 46% of etanercept recipients. The changes in these acute phase reactants during the study demonstrate statistical significant improvement in both at the 12 and 24 week time point (**Table 15**). This improvement is also seen in the number of subjects whose values enter the normal range. At 24 weeks of treatment, the number of placebo recipients with ESR and CRP in the normal range was unchanged but the number among the etanercept recipients had increased to approximately 84%.

Table 15 Other Endpoints: Acute Phase Reactants

Acute Phase Reactants					
Mean (median) Values and Percent Improvement from Baseline					
	Mean (median) Values		**Mean (median) Percent Improvement from Baseline***		
Parameter	**Placebo N = 139**	**Etanercept N = 138**	**Placebo N = 139**	**Etanercept N = 138**	**P-value†**
ESR (mm/hr)‡					
Baseline	**25 (17)**	**26 (23)**			
12 weeks	**26 (16)**	**13 (9)**	**-19 (0)**	**18 (60)**	**< 0.0001**
24 weeks	**26 (19)**	**11 (7)**	**-23 (0)**	**42 (60)**	**< 0.0001**
CRP (mg/dL)**					
Baseline	**2 (1)**	**2 (1)**			
12 weeks	**2 (1)**	**1 (0.2)**	**-143 (-5.4)**	**10 (69)**	**< 0.0001**
24 weeks	**2 (1)**	**<1 (0.3)**	**-96 (0)**	**38 (73)**	**< 0.0001**

‡ Erythrocyte sedimentation rate (ESR) normal range: 1–17 mm/hr for men; 1–25 mm/hr for women.
**C-reactive protein (CRP) normal range: 0–1.0 mg/dL.

Assessor Global Assessments

In the same manner as Physician Global Assessments have been used to complement Patient Global Assessments for therapeutic measurements in other rheumatologic disorders, they have been studied in Ankylosing Spondylitis and were analyzed in this study. As demonstrated in (**Table 16**), the Assessor Global Assessment showed statistically significant improvement among the etanercept recipients at both the 12 and the 24 week time points.

Table 16 Other Endpoints: Assessor Global Assessments

Assessor Global Assessments					
Mean (median) Values and Percent Improvement from Baseline					
	Mean (median) Values		**Mean (median) Percent Improvement from Baseline**		
Parameter	**Placebo N = 139**	**Etanercept N = 138**	**Placebo N = 139**	**Etanercept N = 138**	**P-value***
Assessor's Global Assessment					
Baseline	**57 (58)**	**54 (57)**			
12 weeks	**48 (50)**	**33 (30)**	**10 (14)**	**34 (45)**	**< 0.0001**
24 weeks	**49 (51)**	**34 (30)**	**6 (13)**	**30 (45)**	**< 0.0001**

* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Exploratory Analysis

ASAS DCART 20 and ASAS DCART 40 Exploratory Analysis

Disease-controlling Anti-rheumatic Therapy (DCART) criteria were proposed by an ASAS advisory group for use in AS in discussions held with the FDA. Two alternative endpoint definitions were proposed and this study pre-specified both as exploratory analyses.

The DCART 20 is a composite score that combines the 4 criteria of the ASAS Response Criteria used in the primary efficacy analysis with 2 additional criteria; improvement in chest expansion (spinal mobility) and CRP (acute phase reactants). The ASAS DCART 20 response requires a 20% improvement in 5 or the 6 criteria, with no worsening in the remaining criterion. For the 4 criteria that DCART shares with ASAS Response Criteria, the same rules apply. For the 2 additional criteria, changes in measurements of chest expansion and CRP were based upon 20% improvement or worsening relative to baseline without requirement for absolute numeric change.

The DCART 40 uses the 4 criteria of the ASAS Response Criteria and does not propose any additional criteria. In this instance, a 40% improvement relative to baseline plus absolute improvement of at least 20 units on 3 of the original ASAS criteria with no worsening in the remaining criterion are necessary.

The results of these exploratory analyses are presented in **(Table 17).** Both the DCART 20 and DCART 40 demonstrated statistically significant improvement of etanercept over placebo at 12 and 24 weeks.

Table 17 Exploratory Analysis: Number(%) Achieving ASAS DCART 20 and ASAS DCART 40

Exploratory Analysis: ASAS DCART 20/40			
Number (%) Achieving ASAS DCART 20 /40 Responses			
	Placebo	**Etanercept**	
DCART-proposed Parameter	**N = 139**	**N = 138**	**P-value***
ASAS DCART 20 (n [%]) at:			
2 weeks	**7 (5)**	**41 (30)**	**< 0.0001**
12 weeks	**11 (8)**	**51 (37)**	**< 0.0001**
24 weeks	**10 (7)**	**46 (33)**	**< 0.0001**
ASAS DCART 40 (n [%]) at:			
2 weeks	**11 (8)**	**38 (28)**	**< 0.0001**
12 weeks	**21 (15)**	**59 (43)**	**< 0.0001**
24 weeks	**18 (13)**	**57 (41)**	**< 0.0001**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Duration and Attainment Delay of ASAS 20 Response

Measurement of ASAS 20 at both 12 and 24 week permits exploration of response dynamics to include treatment response duration and delay. As presented in (**Table 18**) 86% of subjects receiving etanercept who had achieved an ASAS 20 at week12 also had an ASAS 20 response at 24 weeks compared to 66% of placebo. Further, the treatment difference between etanercept and placebo12 week responders continues unchanged at 24 weeks. The percentage of etanercept

recipients who lost ASAS 20 response in the 12 weeks between measurements was less than half of that of placebo recipients and the percentage achieving ASAS 20 for the first time was twice as high (15% versus 7%). This suggests that most patients who achieve an ASAS 20 response on etanercept will achieve that response by 3 months.

Table 18 Duration of ASAS 20 and Delay in Attainment of ASAS 20

Exploratory Analysis: Duration of ASAS 20 and Delay in attainment		
	Placebo	Etanercept
Parameter	N = 139	N = 138
ASAS 20 or higher (n [%]) at:		
12 weeks	38 (27)	83 (60)
24 weeks	32 (23)	80 (58)
ASAS 20 at 12 wks also responders at 24wks	25/38 (66)	71/83 (86)
ASAS 20 at both 12/24 wks/ITT population	25/139 (18)	71/138 (51)
Positive to Negative	13/38 (34)	12/83 (14)
Negative to Positive	7/101 (7)	8/55 (15)

Exploratory Analysis: Impact of Gender, Race and Site on ASAS 20

76% of study participants were male and the treatment difference between etanercept and placebo for men is 38% Etanercept also appears to be beneficial for women but the treatment associated difference appears blunted at 17% (**Table 19**).
The significance of this finding is unknown and may be due to wider confidence intervals due to the small number of females enrolled. The impact of race upon the ASAS 20 is difficult to assess since only 20 non-caucasians were enrolled. Geographic site did not appear to have a significant impact upon the ASAS 20 treatment response (**Table 19**).

Table 19 Exploratory Analysis: ASAS 20 at 12wks by baseline non-disease associated factor

Exploratory Analysis: ASAS 20 Non-disease Associated Factor			
Baseline Characteristic	Status	Placebo n/N (%)	Etanercept n/N (%)
Sex	Male	28/105 (27)	68/105 (65)
	Female	10/34 (29)	15/33 (45)
Race	Caucasian	36/127 (28)	76/130 (58)
	Non-Caucasian	2/12 (17)	7/8 (88)
Site	North American	34/109 (31)	63/106 (59)
	European	4/30 (13)	20/32 (63)

Exploratory Analysis: Impact of Age, Weight and Disease Duration upon ASAS 20 at 12 Weeks

Etanercept administration was associated with superior treatment response in all age groups. However, the treatment response appears to decline steadily as age increases from 74% in subjects <34 to 45% in subjects older than 50 years of age **(Table 20)**. Weight did not appear to have a significant impact upon ASAS 20 responses of etanercept. Despite the apparent impact of age upon response, duration of disease did not appear to have a significant impact upon the ASAS 20 with those with a less than 2.25 year duration of illness having the same ASAS 20 as those with those with a greater than 16 year disease duration **(Table 20)**.

Table 20 Exploratory Analysis: ASAS 20 at 12wk by Age, Weight and Duration of Disease

Characteristic	Placebo N/N (%)	Etanercept N/N (%)
Whole Population	**38/139 (27)**	**83/138 (60)**
AGE		
<34	**12/38 (32)**	**23/31 (74)**
34 to <42	**6/25 (24)**	**24/37 (65)**
42 to <50	**10/35 (29)**	**23/41 (56)**
50+	**10/41 (24)**	**13/29(45)**
WEIGHT		
<68kg	**9/33 (27)**	**16/29 (55)**
68 to <80kg	**9/26 (35)**	**28/45 (62)**
80 to <93kg	**10/40 (25)**	**18/32 (56)**
93+ kg	**10/39 (26)**	**20/31 (65)**
DISEASE DURATION		
<2.25yrs	**16/35 (46)**	**20/34 (59)**
2.25 to <8.75yrs	**8/35 (23)**	**19/34 (56)**
8.75 to <16.25yrs	**4/31 (13)**	**25/38 (66)**
16.25+ yrs	**10/38 (26)**	**19/32 (59)**

Exploratory Analysis: Impact of Concomitant Non-Skeletal Inflammatory Disorders upon ASAS 20 at 12 weeks.

Patients with non-skeletal inflammatory disorders associated with Ankylosing Spondylitis such as uveitis as well as conditions associated with other spondyloarthropathies such as psoriasis were enrolled in this study. The impact of these conditions upon ASAS 20 response was explored. History of Uveitis/Iritis, inflammatory bowel disease and risk of reactive arthritis did not appear to have any adverse impact upon the ASAS 20 response to etanercept **(Table 21).**

Table 21 Exploratory Analysis: ASAS 20 at 12 wks in subjects with Concomitant Non-Skeletal Inflammatory Disorders

Baseline Characteristic	Status	Placebo n/N (%)	Etanercept n/N (%)
Hx Uveitis or Iritis	**No**	**26/96 (27)**	**58/99(59)**
	Yes	**12/43 (28)**	**25/39 (64)**
Hx Psoriasis	**No**	**33/124 (27)**	**78/127 (61)**
	Yes	**5/15(33)**	**5/11(45)**
Hx IBD	**No**	**38/133(29)**	**78/131(60)**
	Yes	**0/6(0)**	**5/7(71)**
Hx bacterial dysentery, urethritis Chlamydia, STD	**No**	**33/126 (26)**	**76/127(60)**
	Yes	**5/13 (38)**	**7/11(64)**

Exploratory Analysis: Impact of prior and or concomitant medications upon ASAS 20 at 12 weeks.

The majority of subjects had history of either prior or concomitant medications. Approximately 31% were receiving concomitant DMARDS and the study was stratified to consider DMARD use. Exploratory analysis of the impact of prior or concomitant medication use did not indicate a significant effect on the ASAS 20 at 12 weeks (**Table 22).** Subjects using NSAIDS appeared to have higher response to etanercept than those without such use but the numbers are small. Of the DMARDS, responses to etanercept were higher among patients receiving concomitant Sulfasalazine compared to other DMARDS. Methotrexate use, however, appeared to be associated with a lower response but again the numbers are small and no definite conclusions can be reached.

Table 22 Exploratory Analysis: ASAS 20 at 12 weeks compared with prior/concomitant medications

Baseline Characteristic	Status	Placebo N/N (%)	Etanercept N/N (%)
NSAIDS w/i 6mo Screening	**No**	**3/11 (27)**	**6/12(50)**
	Yes	**35/128 (27)**	**77/126 (61)**
Corticosteroids w/i 6mo Scr	**No**	**37/119 (31)**	**72/120(60)**
	Yes	**1/20 (5)**	**11/18(61)**
Concomitant DMARD(s)	**No**	**29/96 (30)**	**56/94(60)**
	Yes	**9/43 (21)**	**27/44(61)**
Concomitant sulfasalazine	**No**	**31/109 (28)**	**63/109 (58)**
	Yes	**7/30 (23)**	**20/29 (69)**
Concomitant methotrexate	**No**	**35/122 (29)**	**75/123(61)**
	Yes	**3/17 (18)**	**8/15 (53)**

Exploratory Analysis: Impact of Baseline Disease Severity upon the ASAS 20 at 12 weeks
The impact of baseline disease severity upon the response to etanercept was explored using individual components of the ASAS response criteria and hip involvement, a prognostic factor in ankylosing spondylitis. The superiority of etanercept was preserved for each individual component for both high and low baseline disease severity. There were, however, differences in the magnitude of response and in the treatment difference compared to placebo. For the components of average back pain, patient global assessment, and the last two questions of the BASDAI (inflammation) those demonstrating greater disease severity at baseline had higher percentages of ASAS 20 achievement and wider treatment differences compared to placebo **(Table 23).** For the BASFI, although the treatment difference is higher in the population with greater disease severity, the percentage achieving ASAS 20 was lower **(Table 23).** A possible explanation for these differences may be that the disease severity measured in the first three components has a stronger relationship to inflammation than does the functionality measured in the BASFI. The presence of hip involvement did not appear to have a significant impact upon the ASAS 20 achievement percentages.

Table 23 Exploratory Analysis: ASAS 20 at 12 wks compared with baseline individual disease severity

Baseline Characteristic	Status	Placebo	Etanercept
Average Back Pain-total	**≤ Median =63**	**22/65 (34)**	**40/74 (54)**
	> Median=63	**16/74 (22)**	**43/64 (67)**
Patient Global Assessment	**≤ Median=65**	**22/74 (30)**	**39/68 (57)**
	> Median=65	**16/65 (25)**	**44/70 (63)**
BASFI	**≤ Median=53.4**	**22/61 (36)**	**50/78 (64)**
	> Median=53.4	**16/78 (21)**	**33/60 (55)**
Average last 2 BASDAI	**≤ Median=62.5**	**19/65 (29)**	**43/74 (58)**
	> Median=62.5	**19/74 (26)**	**40/64 (63)**
Hip disease or limited ROM of Hip	**No**	**9/31 (29)**	**27/44 (61)**
	Yes	**29/107 (27)**	**50/85 (59)**

Further exploration of the relationship between baseline disease severity and the percentage of ASAS response was performed to include further refinement of severity measurement as well as treatment duration. As shown in **(Table 24),** at 12 weeks, subjects with baseline back pain measured <50 had the lowest ASAS 20 and treatment difference compared with placebo. ASAS 20 and treatment difference percentages do not increase in a strictly linear manner, however. The highest ASAS 20 and treatment difference percentage were actually found in those with a baseline back pain VAS of between 63 and 76 **(Table 24).** These findings persist at 24 weeks **(Table 24)**.

Table 24 Exploratory Analysis: ASAS 20 at 12/24wks by Baseline Back Pain

Baseline Back pain	Placebo N/N (%)	Etanercept N/N (%)
Week 12		
All	**38/134 (28)**	**83/133 (62)**
<50	**9/26 (35)**	**19/37 (51)**
50 to <63	**13/36 (36)**	**20/32 (63)**
63 to <76	**9/36 (25)**	**24/33 (73)**
76+	**7/36 (19)**	**20/31(65)**
Week 24		
All	**32/121 (26)**	**80/125 (64)**
<50	**10/24 (42)**	**19/33 (58)**
50 to <63	**11/32 (34)**	**18/29 (62)**
63 to <76	**7/34 (21)**	**24/32 (75)**
76+	**4/31 (13)**	**19/31 (61)**

Exploratory Analysis: Impact of HLA B27 upon ASAS Response Criteria

84% of the study population was positive for HLA B27 antigen. Examination of the impact of the presence or absence of this antigen on the ASAS 20/50/70 response rates at 12 and 24 weeks indicate that for the ASAS 20 and ASAS 50 measurements, subjects that were HLA-B27 antigen positive had a better response to etanercept than the entire population **(Table 25)**. Conversely, although consistently higher than placebo in all comparisons, etanercept recipients who were HLA-B27 antigen negative had lower ASAS 20 and 50 response percentages at 12 weeks and 24 weeks compared to those of the HLA-B27 positive patients **(Table 25)**. The ASAS 70 determinations in etanercept recipients appeared to be approximately the same in the two subpopulations at both times. The explanation for this apparent blunting of the ASAS 20/50 response at 12 and 24 weeks is unknown but it should be kept in mind that only small numbers of HLA-B27 antigen negative patients were enrolled.

Table 25 Exploratory Analysis: ASAS 20/50/70: HLA B27 Known

Secondary Endpoints: Impact HLA-B27				
	HLA B27 Positive		**HLA B27 Negative**	
	Placebo	**Etanercept**	**Placebo**	**Etanercept**
Parameter	**N = 109**	**N = 108**	**N = 19**	**N = 21**
ASAS 20 (n [%]) at:				
12 weeks	**31 (28)**	**70 (65)**	**5 (26)**	**8 (38)**
24 weeks	**26 (24)**	**67 (62)**	**3 (16)**	**9 (43)**
ASAS 50 (n [%]) at:				
12 weeks	**14 (13)**	**53 (49)**	**3 (16)**	**6 (29)**
24 weeks	**11 (10)**	**49 (45)**	**2 (11)**	**7 (33)**
ASAS 70 (n [%]) at:				
12 weeks	**7 (6)**	**33 (31)**	**2 (11)**	**6 (29)**
24 weeks	**5 (5)**	**31 (29)**	**2 (11)**	**6 (29)**

Safety Analyses

Overview of Adverse Events

Approximately 75% of patients in both study arms experienced one or more adverse events (**Table 26**). Overall, injection site reactions, accidental injury and infections occurred more frequently in the etanercept arm than in the placebo. The incidence rate for injection site reactions and infections was similar to those reported in the package insert. Study drug dose modification was accomplished by skipping administration of scheduled dose. At least one dose of study drug was skipped for adverse events in 3 placebo recipients and 14 etanercept recipients. Infection was the associated adverse event in 1 of 3 placebo and 9 of 14 etanercept recipients. No study drug was skipped for a laboratory abnormality.

Table 26 Adverse Events in ≥ 5% of Patients

Adverse Events of All Intensities in ≥5% of Patients in Either Treatment Group		
	Proportions of Patients (n [%])	
	Placebo	**Etanercept**
Event	**N = 139**	**N = 138**
Any adverse event	**105 (76)**	**99 (72)**
Infections	**42 (30)**	**57 (41)**
Injection site reaction	**13 (9)**	**41 (30)**
Injection site ecchymosis	**23 (17)**	**29 (21)**
Headache	**16 (12)**	**19 (14)**
Accidental injury	**6 (4)**	**17 (12)**
Diarrhea	**13 (9)**	**11 (8)**
Rash	**9 (7)**	**11 (8)**
Dizziness	**3 (2)**	**8 (6)**
Rhinitis	**9 (7)**	**8 (6)**
Abdominal pain	**7 (5)**	**8 (6)**
Nausea	**7 (5)**	**7 (5)**
Asthenia	**7 (5)**	**5 (4)**

The incidence of severe and serious adverse events as well as discontinuations for adverse events were numerically higher in the etanercept arm compared to the placebo arm **(Table 27**). There were no discontinuations for laboratory abnormalities.

Table 27 Tabulation of Important Safety Outcomes

Safety Outcomes	Placebo N=139 n/N %	Etanercept N=138 n/N %
Serious Adverse Events	**5 (4)**	**9 (7)**
Withdrawals for Safety	**1(1)**	**7 (5)**
Grade 3/4 Adverse Events/ Infections	**4(3)**	**14 (10)**
Grade 3/ 4 Abnormal Laboratory	**0 (0)**	**2*(1)**

*** 1 Grade 3 Low ANC, 1 Grade 3 Low Lymphocytes**

Serious Adverse Events

10 SAE occurred in 9 etanercept recipients and 5 SAE occurred in 5 placebo patients (**Table 28).** Infections and accidental injury occurred in both study arms but were more frequently encountered among the etanercept patients. Serious infections will be discussed separately. Of the remaining Serious Adverse Events in the etanercept group, one patient developed a febrile reaction with rash suggestive of a hypersensitivity reaction, another developed transient unilateral lymphadenopathy (with equivocal PPD positivity) that resolved without treatment and another patient with a past history of ulcerative colitis developed pancolitis while on treatment that necessitated study discontinuation.

Table 28 Serious Adverse Events

Patient no.	Sex/Age	D/C Date	Cause	Grade	Comments
Placebo					
163	**M/45**	**25**	**Industrial Accident**	**3**	**Hospitalized**
245	**M/29**	**164**	**Viral Infection**	**2**	**Hospitalized**
268	**M/49**	**141**	**Suicide Attempt**	**4**	**Hx Major Psychiatric Dz**
562	**M/50**	**15**	**MVA back injury**	**3**	**D/C LOE**
572	**F/48**	**100**	**Chest Pain**	**2**	**Hospitalized w/ recur CP r/oMI**
Etanercept					
158	**M/53**	**23**	**Febrile Reaction**	**3**	**3hr p w/rash**
167	**M/60**	**141**	**Lymphadenopathy**	**2**	**+/- PPD -INH prophylaxis**
191	**M/28**	**94**	**Cellulitis insect bite**	**3**	**Hospitalization**
241	**M/43**	**129**	**Vertebral Fx MVA**	**3**	**Hospitalization**
269	**M/64**	**71**	**Fibular fracture fall**	**3**	**Multiple Med-problems**
513	**M/34**	**82**	**Cellulitis cat bite**	**3**	**Hospitalized**
515	**F/49**	**43**	**Fx Elbow fall**	**3**	**Hospitalized**
559	**M/44**	**110**	**Pancolitis UC**	**3**	**Hx IBD switch TNF**
580	**M/56**	**144**	**Intestinal Obstruction**	**3**	**Prior Surgery Adhesions**

Infections

As previously shown in **(Table 28),** there were 3 infections that were considered serious, one in the placebo arm and the other two in the etanercept arm. In both instances in the etanercept arm, the serious infections both involved cellulitis associated with an antecedent injury; one an insect bite, the other a cat bite, and both required intravenous antibiotics to control the infection. Staphlococcus aureus was recovered in the insect bite cellulitis, the presumed bacterial cause of the cat bite related cellulitis was not recovered.

Infections of all intensities were more common in etanercept recipients. The predominant cause appears to be the greater incidence of upper respiratory tract infections **(Table 29).**

Table 29 Infections of All Intensities in ≥ 5% of Patients

Infections of All Intensities in ≥ 5% of Patients in Either Treatment Group		
	Proportions of Patients (n [%])	
	Placebo	Etanercept
Event	N = 139	N = 138
Any infection	42 (30)	57 (41)
Any infection except URI	28 (20)	33 (24)
Upper respiratory infection	16 (12)	28 (20)
Flu syndrome	10 (7)	5 (4)

If patients treated with oral or parenteral systemic antimicrobials are compared between etanercept and placebo, the important contribution of bacterial causes to the increased incidence of URI becomes apparent **(Table 30**). Dental infections and sinusitis in particular appeared to be numerically more prevalent among etanercept recipients than in placebo recipients.

Cellulitis requiring antibiotics was also more prevalent in the etanercept group but the numbers were small, the higher incidence of intravenous antibiotics in the etanercept group was largely caused by 3 SAE: the two serious infections (previously mentioned) and the patient with exacerbation of ulcerative colitis **(Table 30**).

Table 30 Infections Requiring Oral or Parenteral Systemic Antimicrobials

Infections Requiring Oral or Parenteral Systemic Antimicrobial Therapy (AMT)	Placebo n/N %	Etanercept n/N %
Total number of subjects receiving AMT/ Total Study Population	**21/139 (15)**	**27/138 (20)**
URI/Dental/Sinusitis/Otitis Media	**9/21 (43)**	**14/27 (52)**
Bronchitis/Pneumonia	**3/21 (14)**	**3/27 (11)**
UTI or GYN	**3/21 (14)**	**3/27 (11)**
Cellulitis	**1/21 (5)**	**3/27 (11)**
GI/Colitis	**1/21 (5)**	**2/27 (7)**
Antibiotic Prophylaxis	**4/21 (19)**	**4/27 (15)**
IV Antibiotics	**0/21 (0)**	**3/27 (11)**

Study Withdrawals for Safety

There was one withdrawal from study for safety in the placebo arm compared to seven withdrawals in the etanercept arm (**Table 31**). There is overlap between safety withdrawals and patients with SAE since some of these were discontinued. Of the seven withdrawals in etanercept recipients, 4 were for bowel related. One of these was a bowel obstruction secondary to surgical adhesions, the other three were for symptoms suggestive of inflammatory bowel disease (IBD). One episode occurred in an individual with medical history suggestive of IBD prior to enrollment, the other two did not give a history of IBD prior to enrollment but upon questioning, had histories that were suggestive of IBD. Two of the three episodes were diagnosed as inflammatory bowel disease, one was a recurrence in the previously diagnosed patient, and the other was a new diagnosis. The third patient was evaluated and colonoscopic evaluation did not reveal IBD; his diarrhea was attributed to study drug with hemorrhoidal bleeding. Of the 6 individuals with history of IBD prior to enrollment in the placebo arm, none were withdrawn for flare of IBD. Of the 7 individuals in the etanercept arm with a history consistent with IBD prior to enrollment, 3 developed bloody diarrhea of sufficient severity to withdraw from study, two diagnosed as having a flare of IBD.

Table 31 Study Withdrawals for Safety

Patient no.	Sex/Age	D/C Date	Cause	Grade	Comments
Placebo					
268	**M/49**	**141**	**Suicide Attempt**	**4**	**Hx Major Psychiatric Dz**
Etanercept					
123	**M/30**	**29**	**LGI Bleed Hemorr Negative IBD**	**2**	**Hx c/w IBD**
158	**M/53**	**23**	**Febrile Reaction**	**3**	**3hr p w/rash**
241	**M/43**	**129**	**Vertebral Fx MVA**	**3**	**Surgical Intervention**
253	**M/54**	**54**	**Ileitis from Crohns**	**1**	**Hx IBD switch TNF**
269	**M/64**	**71**	**Fibular fracture fall**	**3**	**Multiple Med-problems**
559	**M/44**	**110**	**Pancolitis UC**	**3**	**Hx IBD switch TNF**
580	**M/56**	**144**	**Intestinal Obstruction**	**3**	**Prior Surgery Adhesions**

Grade 3 and 4 Adverse Events not considered to be SAE

6 patients, one in the placebo arm and the other 5 in the etanercept arm developed Grade 3 Adverse Events (there were no grade 4) **(Table 32)**. Two in the etanercept arm and one in the placebo experienced elevated blood pressure, one in each arm due to changes in pre-study anti-hypertensives, the remaining etanercept patient developed hypertension for the first time which was easily medically managed. The two remaining etanercept patients developed severe neurologic adverse events; one a 12 day migraine headache (prior history of migraines) and the other a grand mal seizure which was ultimately attributed to a abrupt withdrawal from chronic lorazepam and oxycodone administration. Seizures are mentioned in the current package insert under Warnings, neurologic.

Table 32 Grade 3/4 Adverse Events/Infections Not SAE

Patient no.	Sex/Age	D/C Date	Cause	Grade	Comments
Placebo					
119	**F/52**		**Hypertension**	**3**	**Change in Hypertension Rx**
Etanercept					
126	**F/30**	**35**	**Migraine x12days**	**3**	**Completed Study**
238	**M/32**	**59**	**Gran Mal SZ**	**3**	**Abrupt d/c Valium**
253	**M/54**	**94**	**Hypertension**	**3**	**Change in Hypertension Rx**
505	**F/50**	**16**	**Asthma/Dehydration**	**3**	**Hx Asthma required ER visit**
523	**F/42**	**42**	**Hypertension**	**3**	**New Hypertension**

Laboratory Abnormalities

Many of the patients enrolled in both arms of this study had Grade 1 and 2 laboratory abnormalities at baseline. Absolute neutrophil counts (ANC) were elevated in 27%, lymphocytes were low in 26%, hemoglobin was low in 18%, platelets were high in 32%, liver associated enzymes were elevated in 5-9%, urine proteinuria was present in 2-5% (**Table 33)**. During the study, these values remained stable in the placebo recipients but some did change in the etanercept recipients. High ANC decreased by 10%, low Lymphocytes decreased by 12%, low hemoglobin decreased by 10%, and high platelet counts decreased by 19% **(Table 33).** All of these changes are compatible with the anti-inflammatory activity of etanercept on acute phase reactants. Liver associated enzymes were essentially unchanged. Etanercept antibodies were detected in 2.2% of etanercept recipients. None of these anti-etanercept antibodies were neutralizing.

There were 2 Grade 3 laboratory abnormalities detected in the etanercept arm **(Table 27**). Both involved leukocytes, one patient had a grade 3 low ANC and another patient had a Grade 3 low lymphocyte count. Both of these were transient and study drug was continued. Antibodies to etanercept were detected in 3/136 (2.2%) of etanercept recipients **(Table 33)**. There were no associated etanercept neutralizing antibodies detected.

Table 33 Laboratory Abnormalities Prior and During Study

	Placebo				Etanercept 25mg BIW			
Laboratory Values	**Baseline**		**During Study**		**Baseline**		**During Study**	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
ANC High	**38/138**	**28**	**31/138**	**23**	**37/138**	**27**	**23/136**	**17**
ANC Low	**2/138**	**1**	**2/138**	**1**	**1/138**	**1**	**5/136**	**4**
Lymphocytes Low	**32/138**	**23**	**36/138**	**26**	**40/138**	**29**	**23/136**	**17**
Hemoglobin Low	**25/138**	**18**	**31/138**	**23**	**26/138**	**19**	**12/136**	**9**
Platelets High	**48/138**	**35**	**43/138**	**31**	**40/138**	**29**	**13/136**	**10**
Platelets Low	**0/138**	**0**	**0/138**	**0**	**0/138**	**0**	**3/136**	**2**
SGOT High	**7/138**	**5**	**7/138**	**5**	**5/138**	**4**	**10/135**	**7**
SGPT High	**13/139**	**9**	**10/138**	**7**	**13/138**	**9**	**15/135**	**11**
Urine Proteinuria	**3/138**	**2**	**6/135**	**4**	**7/138**	**5**	**5/136**	**4**
Etanercept Antibodies	**N/A**		**N/A**		**0/136**	**0**	**3/136**	**2.2**

Conclusions

Efficacy

In study 016.0037, etanercept 25mg sc biw was superior to placebo in the achievement of ASAS 20 Response Criteria response at 12 and 24 weeks in patients with active Ankylosing Spondylitis. The treatment difference is an absolute 33%, which is statistically significant at a level of $p < 0.0001$. The treatment difference is retained at 24 weeks. Favorable treatment differences with etanercept at higher levels of ASAS Response were also statistically significant at both 12 and 24 weeks.

Responses for all four domains of the ASAS Response Criteria also supported the superiority of etanercept. The fifth domain recommended by the ASAS Working Group, Spinal Mobility was measured and found to be statistically superior to placebo. Etanercept recipients experienced statistically significant improvement in numbers of tender peripheral joints but not in improvement in numbers of swollen joints. Acute phase reactants ESR and CRP were statistically improved in etanercept recipients compared to placebo recipients.

Exploratory analyses indicated that other proposed Ankylosing Spondylitis Clinical Response Criteria such as DCART 20 and DCART 40 also supported etanercept's superiority over placebo at 12 and 24 weeks.

All subgroup analyses performed indicated that etanercept was superior to placebo although increasing age, female gender, being HLA-B27 negative, having concomitant psoriasis all appeared to be associated with some blunting of the benefit. The use of DMARDS did not appear to affect the treatment difference.

Safety

. Adverse events observed at a higher rate in etanercept recipients were injection site reactions, accidental injury and infections. Serious Adverse Events were similar in both study arms. Infections

of all intensities were more common in etanercept recipients predominantly due to increases in numbers of upper respiratory tract infections. Although the numbers are small, there was a notable difference between safety withdrawals of the two study arms. There were 7 safety withdrawals for etanercept versus 1 for placebo. Of the 7, 4 were for bowel symptoms. 3 of the 4 were for symptoms consistent with inflammatory bowel disease (IBD) of which 2 were diagnosed as IBD. The significance of this is unknown.

Summary of Study CSR-47687

Study Title

"MULTICENTRE, DOUBLE-BLIND, PARALLEL ARM, PLACEBO-CONTROLLED,RANDOMISED PHASE 3 STUDY OF ETANERCEPT IN THE TREATMENT OF PATIENTS WITH ANKYLOSING SPONDYLITIS"

Study Design

Study 47687 was a randomized, multi-center, international, double blinded, placebo controlled phase 3 study of etanercept versus placebo in 84 patients with active ankylosing spondylitis. Subjects were randomly assigned to one of two treatment arms: etanercept 25mg sc biw or placebo on a 1:1 basis. Subjects were treated for a total of 12 weeks with the primary endpoint of achievement of ASAS 20 response criteria. There were 15 days of safety follow-up. Randomization was stratified for the presence of DMARDS approved for use in the study (Sulfasalazine, Methotrexate and Hydroxychloroquine).

Dosing and Dosing Modification

Etanercept 25mg or placebo was administered sc twice per week at a fixed dose for 12 weeks in patients with active AS who met eligibility criteria. There was no provision for dose modification of the study drug other than skipping administration of a dose of study drug. Patients who developed a Grade 3 or 4 adverse event thought to be related to the study treatment could suspend study drug for one week but if 4 consecutive doses of study drug were missed, the subject was withdrawn from study.

Study Population

Men and women, outpatients, between 18 and 70 years of age with AS, as defined by the modified New York Criteria for Ankylosing Spondylitis which was active at the time of enrollment as defined by:

- visual analog scale (VAS) values ≥ 30 (on a scale of 0–100) for the following parameter:
- Average of duration and intensity of morning stiffness

PLUS VAS values ≥ 30 for 2 of the following 3 parameters:

- patient global assessment
- average of VAS values for nocturnal back pain and total back pain
- average of 10 questions on the BASFI.

Excluded were subjects with:

Complete Ankylosis of the spine

Use of DMARDS other than Sulfasalazine, Methotrexate or Hydroxychloroquine
Previous Receipt of Etanercept or other TNFα-blocking agents
Dose of prednisone > 10mg/d or changed within 2 weeks of baseline evaluation
Dose of NSAIDS changed within 2 weeks of baseline or multiple NSAIDS in use
Significant abnormality in chemistry or hematology profiles
Significant concurrent medical conditions or events

Primary Efficacy Outcome

The primary efficacy outcome was determined at 12 weeks of treatment using the following ASAS Response Criteria

- Primary Efficacy Endpoints:
  ASAS Response Criteria (ASAS 20) already defined in study 016.0037 on page 6 at 12 weeks.

Secondary Efficacy Outcomes:

Secondary Efficacy Outcomes included:

The ASAS Response Criteria of 50% and 70% improvement at week 12 which were defined in study 016.0037 on page 6

-Additional analysis of ASAS response at Week 12

- Partial Remission
  Frequency and time to the ASAS definition of partial remission defined on page 7
- Highest ASAS Level Achieved defined on page 7

Individual components of the ASAS Instrument

- Patient global assessment
- Nocturnal back pain, total back pain, and the average of the nocturnal back pain and total back pain scores
- The BASFI and its independent components
- The BASDAI and its independent components

Components of Other AS Instruments

- Spinal mobility (change and percent change from baseline) assessed by:
  - modified Schober's test
  - chest expansion score
  - occiput-to-wall measurement.
- Peripheral tender joints and swollen joint count (change and percent change from baseline).
- Laboratory assessment of inflammation (CRP and ESR), change and percent change from baseline.
- Patient-reported improvement in AS at 2 weeks (percent of patients).
- Assessor global assessment (change and percent change from baseline).

Withdrawal for Lack of Efficacy

Patients could be discontinued from study treatment for lack of efficacy defined as failure to improve 3of 4 ASAS Response Criteria by 10% or more at week 8 (and 12) and at early termination visit.

Clinical and Laboratory Evaluations
Patients were assessed for both efficacy and safety at weeks 2,4,8,12 (or Early Termination). Safety was additionally assessed at the 15-day follow-up. All components of the ASAS Response Criteria as well as Assessor global score and blinded joint assessment were performed at these times. Physical examination including vital signs as well as measurements of spinal mobility were performed at those visits. Laboratory evaluation including Chemistry profile, urinalysis were scheduled to be performed at baseline, weeks 4 and 12. ESR and C-reactive Protein were to be performed with each efficacy/safety visit except for the 15 day follow-up. All laboratory tests except ESR were performed centrally and all results were withheld from the investigator until after the study was un-blinded

Statistical Analyses

Primary efficacy analysis
The primary efficacy population was the modified Intention to Treat population which was defined as all subjects randomized and who received at least one dose of study medication
The primary efficacy endpoint was the number of responders at week 12 as determined by the ASAS response criteria for improvement in AS. The etanercept and placebo groups were compared by using the Mantel-Haenszel test stratified by presence or absence of concomitant DMARDs. All patients who withdrew before 12 weeks were considered non-responders for this endpoint.

Secondary analyses:
Secondary endpoints were the number of responders at week 12 as determined by the ASAS 50% and 70% response criteria. These endpoints were analyzed as described previously for the primary efficacy endpoint (Fisher's exact test was substituted if more appropriate). An additional analysis of ASAS responses at week 12 was performed by classifying patients on a scale of 1 to 4 according to their highest response status with respect to ASAS 20%, 50%, and 70% endpoints. Values assigned were 1 for ASAS 20% non-responders, 2 for ASAS 20% responders, 3 for ASAS 50% responders, and 4 for ASAS 70% responders. Scores were compared between the 2 treatment groups by using the stratified rank test. Changes (and percentage changes) from baseline in the individual components of the ASAS Working Group criteria for response (VAS patient global assessment, VAS total and nocturnal pain, BASFI, and BASDAI), spinal mobility measures, VAS physician global assessment, complete joint assessment, evaluation of hip involvement, and laboratory assessments of inflammation were compared between the 2 treatment groups by using the stratified rank test. The stratified rank test was performed using the Cochran-Mantel-Haenszel test with the modified ridit option.
Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analysis
The PK-PD relationship between etanercept serum concentrations and clinical efficacy was evaluated in this patient population.

Major Protocol Amendments
There were no major protocol amendments

Study Results
The study was conducted entirely in 8 European Countries with 14 centers participating.

Patient Disposition

A total of 84 patients were enrolled in the study and all 84 patients received study drug. Eighty-two (82) patients completed 12 weeks of treatment. Two patients, both in the etanercept arm withdrew from the study. 1 patient did not meet disease activity eligibility criteria and the other withdrew his consent **(Table 34).**

Table 34 Study Completion at 12 weeks

Study Completion Status at 12 Weeks		
	Placebo	**Etanercept**
	(N = 39)	**(N = 45)**
Patient Status	**n (%)**	**n (%)**
Completed 12 weeks in study	**39 (100)**	**43(96)**
Discontinued study due to:		
Lack of disease activity	**0 (0)**	**1 (<1)**
Patient refusal	**0 (0)**	**1 (<1)**

Patient Demographics

The mean age of study participants was approximately 43 and was 4 years older in the etanercept recipients. The study excluded pediatric patients and there was an upper age limit of 70 years of age. The mean weight of participants was 74 kg for placebo recipients and 76 kg for etanercept recipients.

Approximately 78% of the participants were male which corresponds to the higher prevalence of AS in men. More than 93% of the participants were Caucasian, minority participation was low and similar in both arms (**Table 35)**.

Table 35 Population Demographics

Demographic Characteristics		
	Placebo	**Etanercept**
Characteristic	**N = 39**	**N = 45**
Mean age in years	**40.7**	**45.3**
Male (n [%])	**30(77)**	**36(80)**
Race (n [%]):		
Caucasian	**37(95)**	**42 (93)**
Asian	**0 (0)**	**1 (2)**
Other	**2 (5)**	**2 (4)**
Mean weight (kg)	**73.7**	**76.1**

Baseline Disease History

The mean duration of ankylosing spondylitis was higher in the etanercept recipients than in the placebo recipients. The percentage of HLA-B27 antigen positivity was similar in both arms. The majority of participants had a history of NSAIDS and DMARDS usage although the percentage was higher for both in the etanercept recipients. A similar percentage of participants in both arms had a history of concomitant corticosteroid usage. Approximately 40% of participants in both arms were on concomitant DMARDS. Sulfasalazine was the most common DMARD in both arms **(Table 36).**

Table 36 Baseline Disease History

Baseline Disease History		
	Placebo	**Etanercept**
Mean duration of AS in years	**10**	**15**
Median duration of AS in years	**7**	**14**
HLA B-27 positive	**34 (87)**	**38 (88)**
Prior NSAIDS	**36(92)**	**44 (98)**
Prior DMARDS	**24 (62)**	**34 (76)**
Concomitant therapy baseline (n [%]):		
Any DMARD	**16 (41)**	**16 (36)**
Sulfasalazine (SSZ)	**11 (28)**	**11 (24)**
Methotrexate (MTX)	**5 (13)**	**6 (13)**
Hydroxychloroquine (HCL)	**1 (3)**	**0**
Oral Corticosteroids	**6 (15)**	**7 (16)**

Baseline Disease Activity

The level of baseline disease activity as measured by the 4 ASAS domains was of moderate intensity and was well balanced between the two study arms **(Table 37)**. Spinal mobility measurements demonstrated less mobility in the etanercept arm especially in the occiput to wall measurement **(Table 37).** The remainder of baseline measurements of AS components, the physician global assessment, and the acute phase reactants indicated moderate intensity that was balanced across the study arms **(Table 37)**.

Table 37 Baseline Disease Activity

Baseline Disease Activity		
	Placebo	Etanercept
Characteristic	N = 39	N = 45
Mean baseline ASAS components (range):		
Patient global assessment	63(31-86)	66 (26-100)
Nocturnal and total back pain	56 (10-100)	60 (0-100)
BASFI	57 (18-82)	60 (14-100)
Inflammation	59 (36-87)	61 (27–100)
Mean baseline other study AS components		
Physician Global Assessment	58 (15-100)	56(18-87)
Erythrocyte Sedimentation Rate	33 (4-100)	31(1-108)
C-Reactive Protein, mg/L	24 (4-227)	19(4-63)
Chest Expansion Score, cm	3.9 (1-11)	3.3(.5-8)
Schober's Test, cm	12.8 (11-16)	12.2 (11-15)
Occiput to Wall Measurements	4.6 (0-21)	7.3 (0-23)

Extra-Spinal Inflammatory Signs/Symptoms

There was some imbalance between the study arms in terms of extra-spinal inflammatory signs and symptoms. The percentage of participants with ocular inflammation, uveitis, urethritis and psoriasis was higher among the etanercept participants than in the placebo (**Table 38).** The only extra-spinal factors that appeared to be well balanced between the two arms was a history of inflammatory bowel disease and a sexually transmitted disease **(Table 38)**.

Table 38 Extra-Spinal Articular Inflammatory Symptoms

Extra-Spinal/Articular Inflammatory Symptom	Placebo n/N %	Etanercept n/N %
Ocular Inflammation	5/39 (13)	9/45 (20)
Non-Infectious Conjunctivitis	2/39 (5)	4/45 (9)
Uveitis or Iritis	6/39 (15)	13/45 (29)
Crohns Disease or Ulcerative Colitis	2/39(5)	3/45 (7)
Urethritis	0/39 (0)	3/45 (7)
STD	0/39 (0)	0/45 (0)
Psoriasis	3/39 (8)	10/45 (22)

Primary Efficacy Analysis

The primary efficacy endpoint of this study was the achievement of an ASAS 20 at week 12 using the ASAS Working Group Response Criteria. 60% of etanercept recipients versus 23% of placebo recipients achieved the primary endpoint which was statistically significant difference with a p value of 0.0008 **(Table 39)**.

Table 39 Primary Endpoint Study

Primary Endpoint: ASAS 20 at 12 weeks			
Number (%) Achieving ASAS 20 Response at Week 12			
	Placebo	**Etanercept**	
Parameter	**N = 39**	**N = 45**	**P-value***
ASAS 20 at 12 weeks	**9 (23)**	**27(60)**	**0.0008**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Secondary Efficacy Analysis

In this study, the secondary efficacy analysis includes all the remaining AS measurements including: ASAS 50 and 70 at 12 weeks, highest ASAS response at 12 weeks, achievement of partial remission, analysis of individual components of the ASAS response criteria, spinal mobility parameters, peripheral tender and swollen joints, acute phase reactants, and physician global assessment.

ASAS 50/70 at 12 weeks

Higher levels of response using the ASAS Response Criteria were analyzed. The superior performance of etanercept was again demonstrated in the ASAS 50 measurement with a numerical difference of 49% versus 10% and a p value favoring etanercept of 0.0002 **(Table 40).** Although the etanercept arm had a numerically higher ASAS 70 response than placebo at 24% versus 10%, this value did not achieve statistical significance with a p-value of 0.0973 at 12 weeks **(Table 40).** The explanation for this failure to achieve statistical significance for the ASAS 70 determination is most likely attributable to the small numbers involved.

Table 40 Secondary Endpoints ASAS 20, 50, 70: 2/12 weeks

Secondary Endpoints: ASAS 20/50/70 at 12/24 weeks			
	Placebo	**Etanercept**	
Parameter	**N = 39**	**N =45**	**P-value***
ASAS 20 (n [%]) at:			
2 weeks	**3 (8)**	**24 (53)**	**0.0000**
12 weeks	**9 (23)**	**27 (60)**	**0.0008**
ASAS 50 (n [%]) at:			
2 weeks	**1 (3)**	**11 (24)**	**0.0046**
12 weeks	**4 (10)**	**22 (49)**	**0.0002**
ASAS 70 (n [%]) at:			
2 weeks	**0 (0)**	**6 (13)**	**0.0183**
12 weeks	**4 (10)**	**11 (24)**	**0.0973**
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Highest ASAS Response at week 12

Analysis of highest ASAS response achieved indicates that among the patients whose highest response was ASAS 20, that is they never achieved ASAS 50 or ASAS 70, the numbers and

percentages are similar in both study arms. Higher proportions of etanercept treated patients achieved higher level (ASAS 50, 70) responses **(Table 41).**

Table 41 Secondary Endpoint: Highest ASAS Responses at weeks 12

Secondary Endpoint: ASAS Highest level of Response			
		Placebo	Etanercept
Time point	Highest level of response	N = 39	N = 45
Week 12	ASAS 20 non-responder	30 (77)	18(40)
	ASAS 20 responder	5 (13)	5 (11)
	ASAS 50 responder	1 (3)	14 (31)
	ASAS 70 responder	3 (8)	8 (18)

Partial Remission

As previously indicated, partial remission was defined as achievement of a disease activity level <20 on VAS in all 4 ASAS domains. In this study, although the etanercept recipients have numerically higher partial remission rates than placebo, especially early in the study (2weeks), the differences do not reach statistical significance **(Table 42).**The explanation for this is not known but probably relates to the small number of patients achieving partial remission in both arms.

Table 42 Secondary Endpoint: Achievement of Partial Remission

Secondary Endpoint: ASAS Partial Remission			
	Placebo	Etanercept	
	N = 39	N = 45	
Time point	n (%)	n (%)	P-value*
Week 2	0 (0)	4 (9)	0.0573
Week 12	4 (10)	8 (18)	0.3457
Any time during the study	5 (13)	12 (26)	0.1246
* P-value determined by Cochran-Mantel-Haenszel row means test.			

Individual Components of ASAS Response Criteria

Response data corresponding to each of the components of the 4 domains of the ASAS Response Criteria were individually analyzed. The components analyzed using a Visual Analog Scale were: patient global assessment, average of nocturnal back pain and total back pain, the average of the 10 questions of the BASFI (function) and the last two questions of the BASDAI (inflammation). The

results of this analysis indicated that for each component, etanercept recipients had a statistically significantly greater improvement than placebo recipients **(Table 43).**

Table 43 ASAS Individual Components

Individual ASAS Components					
Mean Values and Percent Improvement from Baseline					
	Mean Values		**Percent Improvement from Baseline**		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Parameter	**N = 39**	**N = 45**	**N = 39**	**N = 45**	
Patient's Global Assessment	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	
Baseline	**63**	**66**			
12 weeks	**54**	**38**	**13**	**37**	**0.0107**
Average of Nocturnal Back Pain/ Total Back Pain	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**56**	**60**			
12 weeks	**51**	**31**	**6**	**43**	**0.0003**
BASFI	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**57**	**60**			
12 weeks	**54**	**40**	**3**	**35**	**0.0003**
BASDAI	**Placebo**	**Etanercept**	**Placebo**	**Etanercept**	**P-value**
Baseline	**63**	**68**			
12 weeks	**53**	**36**	**16**	**43**	**0.0025**

Spinal Mobility Parameters

Assessment for Spinal Mobility using the modified Schober's test, chest expansion and occiput to wall measurement and these data are presented in (**Table 44).** In this study, although in all three measurements, the percentage of improvement in the etanercept recipients was consistently numerically higher than placebo, only in the Schober's test did that superiority reach statistical significance at12 weeks **(Table 44).** Measurement of chest expansion which is the spinal mobility parameter selected for the DCART 20 **(Table 17)** demonstrated the least significant p-value of the three. The explanation for these spinal mobility parameter data is not known but the relatively short duration of treatment(12 weeks) and the small number of patients are likely contributants.

Table 44 Other Endpoints: Spinal Mobility Parameters

Spinal Mobility Parameters:					
Mean Values and Percent Improvement from Baseline					
	Mean Values (cm)		**Percent Improvement from Baseline***		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 39**	**N = 45**	**N = 39**	**N = 45**	**P-value†**
Modified Schober's test					
Baseline	**2.8**	**2.2**			
12 weeks	**2.7**	**2.7**	**-1.3**	**36**	**0.0085**
Chest expansion					
Baseline	**3.9**	**3.3**			
12 weeks	**4.1**	**3.8**	**9**	**30**	**0.8695**
Occiput-to-wall Measurement					
Baseline	**4.6**	**7.3**			
12 weeks	**4.0**	**6.2**	**7**	**13**	**0.0650**
* Patients with a score of zero at baseline were not included in the analysis of percent improvement from baseline. The number of patients with a zero baseline score varied, depending on the parameter of interest.					
† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent Improvement from baseline.					

Peripheral Tender and Swollen Joint Counts

As was seen in the previously described study, the response rates of peripheral tender and swollen joints are lower than those of other domains. Treatment difference favoring etanercept is suggested for both tender and swollen joints, especially for tender joints (**Table 45**). Neither measured difference achieves statistical significance, however. Again, the likely explanations are the small study population and the paucity of any peripheral joint involvement, especially swollen joints among this population. The median values for number of swollen joints was 0 and 3 for tender joints in both arms at baseline. The values seen in **(Table 45)** represent those individuals with swollen and painful joints at baseline.

Table 45 Other Endpoints: Peripheral Tender and Swollen Joint Counts

Peripheral Tender and Swollen Joint Counts					
Mean Values and Percent Improvement from Baseline					
	Mean Values		**Percent Improvement from Baseline***		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 39**	**N = 45**	**N = 39**	**N =45**	**P-value†**
Tender joints					
Baseline	**9.7**	**6.6**			
12 weeks	**8.3**	**3.5**	**14**	**47**	**0.0613**
Swollen joints					
Baseline	**5.1**	**3.6**			
12 weeks	**5.3**	**2.3**	**-4**	**36**	**0.4095**
* Patients with a count of zero at baseline were not included in the analysis of percent improvement from baseline. The number of patients with a zero baseline score varied, depending on the parameter of interest.					
† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent Improvement from baseline.					

Acute Phase Reactants

At baseline the measured acute phase reactants in both arms of the study were elevated with mean ESR/CRP for etanercept and placebo of 31/19 and 33/24 and median ESR/CRP for etanercept and placebo of 27/15 and 26/10 **(Table 46).** During the course of the study, the median values for both ESR and CRP dropped significantly among the etanercept recipients compared to placebo **(Table 46).**

Table 46 Other Endpoints: Acute Phase Reactants

Acute Phase Reactants					
Median Values and Percent Improvement from Baseline					
	Median Values		**Percent Improvement from Baseline***		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 39**	**N = 45**	**N = 39**	**N =45**	**P-value†**
ESR (mm/hr)‡					
Baseline	**26**	**27**			
12 weeks	**29**	**6**	**0**	**80**	**<0.0001**
CRP (mg/dL)**					
Baseline	**9.7**	**15.4**			
12 weeks	**11.7**	**4.0**	**-20**	**70**	**<0.0001**
* Patients with a score of zero at baseline were not included in the analysis of percent improvement from baseline. Some patients in both groups had a baseline score of zero for ESR, but no patients in either group had a baseline score of zero for CRP.					
† P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.					
‡ Erythrocyte sedimentation rate (ESR) normal range: 1–17 mm/hr for men; 1–25 mm/hr for women.					
**C-reactive protein (CRP) normal range: 0–1.0 mg/dL.					

Physician Global Assessments

The Physician Global Assessments performed in this study indicated that etanercept recipients had greater improvement from baseline than did placebo. This treatment difference was statistically significant **(Table 47).**

Table 47 Physician Global Assessments

Physician Global Assessments					
Mean Values and Percent Improvement from Baseline					
	Mean Values		**Percent Improvement from Baseline**		
	Placebo	**Etanercept**	**Placebo**	**Etanercept**	
Parameter	**N = 39**	**N = 45**	**N =39**	**N = 45**	**P-value***
Assessor's Global Assessment					
Baseline	**57.5**	**55.7**			
12 weeks	**46**	**32.6**	**20**	**39**	**0.0321**
* P-value determined by Cochran-Mantel-Haenszel row means test with Modridit option on percent					
Improvement from baseline.					

Safety Analyses

Overview of Adverse Events

Approximately 60% of patients in both study arms experienced one or more adverse events during the 12 weeks of study and 15 days of follow-up **(Table 48).** Overall, injection site reactions, injection site ecchymosis, and asthenia were more prevalent in etanercept recipients than in placebo recipients. In this study, infections occurred with similar incidence in both study arms. Study drug dose modification was accomplished by skipping administration of a scheduled dose.

Table 48 Adverse Events in ≥ 5% of Patients

Adverse Events of All Intensities in ≥5% of Patients in Either Treatment Group		
	Proportions of Patients (n [%])	
	Placebo	Etanercept
Event	N = 39	N = 45
Any adverse event	24 (62)	25 (56)
Infections	13(33)	16(36)
Injection site reaction	6 (15)	15 (33)
Injection site ecchymosis	4 (10)	8 (18)
Headache	5 (13)	6 (13)
Accidental injury	2(4)	0 (0)
Diarrhea	2(5)	2 (4)
Rash	0 (0)	2 (4)
Dizziness	1 (3)	1 (2)
Rhinitis	9 (7)	8 (6)
Abdominal pain	2 (5)	1 (2)
Nausea	4 (10)	3 (7)
Asthenia	1 (3)	5 (11)

There was one serious adverse event, a myocardial infarction in one etanercept patient who also experienced the only Grade 3 Laboratory Abnormality. There were no withdrawals for safety reasons. The number of Grade 3 Adverse Events was low in both arms but was higher in the etanercept arm **(Table 49).**

Table 49 Tabulation of Important Safety Outcomes

Safety Outcomes	Placebo N=39 n/N %	Etanercept N=45 n/N %
Serious Adverse Events	0 (0)	1* (2)
Withdrawals for Safety	0 (0)	0 (0)
Grade 3/4 Adverse Events/ Infections	2 (5)	4 (9)
Grade 3/ 4 Abnormal Laboratory	0 (0)	1* (2)

*The same patient

Serious Adverse Events

There were no deaths during the study. There was only one serious adverse event occurring during the conduct of this trial. The patient a 51 year old man who was a etanercept recipient experienced a

acute myocardial infarction. He received a coronary artery bypass and completed the study (**Table 50**).

Table 50 Serious Adverse Events

Patient no.	Sex/Age	D/C Date	Cause	Grade	Comments
Placebo					
Etanercept					
012-335	**M/51**	**81**	**Myocardial Infarction**	**3**	**Completed Study after CABG**

Infections

The numbers of infections in both study arms was similar. Upper respiratory tract infection was numerically the most common infection in both arms occurring in 3 placebo recipients and 5 etanercept. Flu syndrome was more common in placebo compared to etanercept at 4 to 1, and periodontal abscess was more common in etanercept patients at 3 to 0. Otherwise all infections occurred with nearly identical incidence between the two arms **(Table 51).**

Table 51 Infections of All Intensities in ≥ 5% of Patients

Treatment Emergent Infections in Either Treatment Group		
	Proportions of Patients (n [%])	
	Placebo	Etanercept
Event	**N = 39**	**N = 45**
Any infection	**13 (33)**	**16 (36)**
Any infection except URI	**10 (26)**	**12 (27)**
Upper respiratory infection	**3 (8)**	**5 (10)**
Flu syndrome	**2 (5)**	**1 (2)**

Grade 3 and 4 Adverse Events not considered SAE

There were no Grade 4 Adverse Events in either study arm. The Grade 3 Adverse Events occurring in the etanercept recipients included one episode of asthenia, one of severe headache, one accidental bone fracture and the grade 3 liver function test abnormalities that occurred in the patient who

experienced the myocardial infarction **(Table 52).** These liver function test abnormalities resolved with the discontinuation of the patient's NSAIDS.

Table 52 Grade 3/4 Adverse Events/Infections Not SAE

Patient no.	Sex/Age	Cause	Grade
Placebo			
004-99	**M/61**	**BACK PAIN**	**3**
012-333	**M/27**	**HYPOGLYCEMIA**	**3**
Etanercept			
004-98	**M/40**	**ASTHENIA**	**3**
009-245	**M/43**	**HEADACHE**	**3**
009-247	**F/51**	**BONE FX**	**3**
012-335	**M/51**	**ABN LFTS**	**3**

Conclusion

Efficacy

In study CSR-47687, etanercept 25mg sc biw was superior to placebo in the achievement of ASAS 20 Response Criteria at 12 weeks in patients with active Ankylosing Spondylitis. The treatment difference is an absolute 37%, which is statistically significant at a level of p= 0.0008. At ASAS 50, etanercept also achieved statistical superiority to placebo but not at ASAS 70.

All four domains of the ASAS Response Criteria supported the superiority of etanercept. The fifth remaining ASAS Working Group recommended domain, Spinal Mobility was measured. In this study, only the modified Schober's test determined a statistically significant improvement compared to placebo at 12 weeks. As in Study 016.0037, chest expansion was the spinal mobility parameter that evidenced the least response. Etanercept recipients experienced improvement in numbers of tender and swollen peripheral joints but these improvements were not statistically significant. Acute phase reactants ESR and CRP were statistically improved in etanercept recipients compared to placebo recipients.

Safety

. The only adverse events notably increased in etanercept recipients were injection site reactions, injection site ecchymosis and asthenia. In this study, infections occurred with similar incidence in both study arms. There was only one Serious Adverse Event, no withdrawals for safety and few significant adverse events in either arm.

Summary of Study CSR: 016.0626

Study Title:
"Anti-Tumor Necrosis Factor (TNFR:Fc) in Ankylosing Spondylitis (A Phase 2 Trial)"

Study Design:
Study 016.0626 was a randomized, single center, double blinded, placebo controlled phase 2 study of etanercept versus placebo in conjunction with the use of standard medication for AS in 40 patients with active ankylosing spondylitis. Subjects were randomly assigned to one of two treatment arms: etanercept 25mg sc biw or placebo on a 1:1 basis. Subjects were treated for a total of 16 weeks with a primary endpoint of 20% improvement from baseline in 3 of 5 elements of pre-specified response criteria (with one of the improved measures being spinal pain or morning stiffness) and without worsening in the remaining 2 elements. For patients without joint swelling (one of the 5 measured elements) at baseline, improvement was required in 3 of the remaining 4 elements without concurrent worsening in the remaining one.

Dosing and Dosing Modification:
Etanercept was administered at a dose of 25 mg SC twice weekly. There was no provision for dose modification other than skipping dosage.

Study Population
Men and Women, outpatients, 18 years or older, with AS, as defined by the modified New York Criteria for Ankylosing Spondylitis, Active AS defined by the presence of morning stiffness ≥ 45 minutes, inflammatory back pain, patient and physician global assessment of moderate or more severe disease activity, receiving a stable dose of one of the following regimens for at least one month prior to study without adequate disease control: NSAID, oral glucocorticoids ≤ 10mg/d, Sulfasalazine, Methotrexate, combination of Methotrexate and Sulfasalazine, azathioprine or 6-mercaptopurine.

Excluded were:
- Spondylitis from other forms of seronegative spondyloarthritides including psoriatic arthritis, inflammatory bowel disease, reactive arthritis, and Behçet's disease.
- Previous receipt of etanercept or antibody to TNF.
- Clinical or radiographic evidence of complete ankylosis of the entire spine.
- Presence of significant concurrent disease

Primary Efficacy Outcome
There were 5 pre-specified measures considered in the primary efficacy outcome (AS Response Criteria).
- Patient global assessment: rated on a 5-point scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) over the past week. Improvement was defined as a decrease of 1. Worsening was defined as an increase of 1.
- Nocturnal spinal pain: assessed on a 100 mm VAS of spinal pain at night over the past week. Extremes of the scale were labeled as "none" and "very severe." Improvement was defined as a 20% decrease in number of millimeters on the scale and an increase of 20% over baseline was classified as worsening.

- Duration of morning stiffness: duration of morning stiffness (in minutes) experienced on the day preceding the clinic visit. Improvement was defined as a 20% decrease in the number of minutes and worsening was an increase of 20%.
- Bath Ankylosing Spondylitis Functional Index (BASFI): 10 questions regarding ability to perform specific tasks as measured by VAS with extremes labeled "none" and "very severe." Improvement was defined as a 20% decrease in the combined mean functional index score. Worsening was defined as an increase of 20%.
- Swollen joint score: peripheral joint swelling score (in 44 diarthrodial joints), rated on a 4-point scale (0 = no swelling, 1 = mild [detectable synovial thickening without loss of bony contours], 2 = moderate [loss of distinctness of bony contours], 3 = severe [bulging synovial proliferation with cystic characteristics]). Swollen joint score included bilateral sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, knee, ankle, and metatarsophalangeal joints. An improvement was defined as a decrease in joint swelling score by 20%, and worsening was a 20% increase in swelling score. If the swollen joint score was 0 at baseline, any increase in score was considered worsening.

Secondary Efficacy Endpoints:

- Individual components of response criteria: patient global assessment, nocturnal spinal pain, duration of morning stiffness, BASFI, and swollen joint score examined independently.
- Spinal mobility evaluations: chest expansion, modified Schober's test, and occiput-to-wall measurement
- Joint pain/tenderness score in 44 diarthrodial joints: rated on a 4-point scale (0 = none, 1 = mild [positive response on questioning], 2 = moderate [spontaneous response elicited], 3 = severe [withdrawal on examination]). Joints evaluated included bilateral sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, knee, ankle, and metatarsophalangeal joints.
- Enthesopathy evaluation (Modified Enthesopathy Index)

- Acute phase reactant: erythrocyte sedimentation rate (ESR) at baseline and monthly thereafter.
- Physician global assessment: a VAS of overall disease activity
  Pain assessment: a VAS due to spinal pain over the past week
- Dougados Spondylitis Functional Index (DSFI)
- Krupp's measure of fatigue: comprised of 9 statements relating to fatigue that patients rate from 1 (indicating strong disagreement with the statement) to 7 (indicating strong agreement); the average of the 9 components subjected to analysis.
- Quality of life as measured by the Short Form Health Survey

Ad Hoc Analyses

- 50% and 70% Response
  Responses in clinical criteria at 50 and 70% improvement levels were determined, with 20% worsening maintained as the definition of worsening.

- ASAS Response Criteria (modified)

Statistical Analyses
The primary efficacy analysis was an intent-to-treat analysis that included all patients who were randomized and received study drug. Patients who discontinued study drug prior to the Day 112 assessment were considered non-responders. The 20% response criteria rates for improvement in AS were compared between the etanercept and placebo groups on Day 112 using Fisher's exact test (two tailed). Analyses at other time points were performed in a similar manner and were considered supplemental. Continuous variables, such as the individual components of the response criteria for improvement in AS, and change and percent change from baseline, were compared between placebo and etanercept using Wilcoxon's test. Values at the last available visit were used for the last observation carried forward (LOCF) analysis, for patients with missing data on Day 112. A supplemental analysis based on data only from patients who completed Day 112 was also performed for the primary endpoint.

Synopsis of the Study Results other than Efficacy Determinations

- Study Completion Status at 16 Weeks: between 90-95%
- Baseline Demographics and Disease Characteristics: Similar to phase 3 studies except for mean age 39, Caucasian participation 75%, DMARDS other than Sulfasalazine and Methotrexate used
- Efficacy and Safety Monitoring similar to that of phase 3 studies
- Safety Data similar to that of phase 3 studies

Efficacy Determinations

Primary Efficacy Analysis

The primary efficacy endpoint for this study was the achievement of a 20% response at week 16 using the 5 pre-specified criteria listed above as, AS Response Criteria. At 16 weeks, 75% of etanercept recipients versus 25% of placebo recipients had achieved this primary endpoint, a statistically significant difference with a p-value of 0.01 **(Table 53**).

Table 53 Primary Endpoint

Primary Endpoint: Number (%) Achieving 20% AS Response Criteria			
	Placebo	**Etanercept**	**P-value**
Time point	**N=20**	**N=20**	
Week 12	**5 (25)**	**14 (70)**	**0.01**
Week 16	**5 (25)**	**15 (75)**	**0.01**

Ad Hoc Analysis

This study was commenced prior to the publishing of the ASAS Working Group Response Criteria. The ASAS Response Criteria were applied to the data, however as an ad hoc analysis. In addition, a 50% and 70% response analysis using the pre-specified criteria for this study was performed. Both will be discussed.

Modified ASAS 20/50/70 Response Criteria

The ASAS Working Group Response Criteria were the same as those used in the two prior studies. Modification was required because in this study patient global assessment was scored on a 1-5 scale rather than by VAS and inflammation was represented by the duration of morning stiffness in minutes without assessment of intensity, not by VAS. The following adjustments were performed to convert to the ASAS Response Criteria.

- Patient global assessments scored on a 1 - 5 scale (GAS) were converted to 0 – 100 scale (VAS) by the following formula: VAS = (GAS-1) x 25.
- The duration of morning stiffness was translated to a 0 – 100 score by setting all durations > 120 minutes to 100 and calculating durations < 120 minutes as 5/6 times the duration in minutes.

Additional endpoints that were evaluated using the modified ASAS definition of response included a 50% and 70% response criteria for improvement, with deterioration defined the same as for the 20% response criteria.

Applying the ASAS Response Criteria with the modifications as described above to the data, at 16 weeks the etanercept recipients achieve an ASAS 20 endpoint of 85% versus 25% for the placebo recipients, a highly statistically significant difference with a p-value of 0.0003 **(Table 54**). While both the AS 20 Response Criteria pre-specified for this study and the modified ASAS Response Criteria indicate superiority of etanercept over placebo, the measured treatment difference is greater using the ASAS Response Criteria.

Table 54 Ad Hoc Analysis: ASAS 20, 50, 70

ASAS 20/50/70 for Study 0626			
	Placebo	**Etanercept**	
Parameter	**N = 20**	**N = 20**	**P-value***
ASAS 20 (n [%]) at:			
12 weeks	**5 (25)**	**13 (65)**	**0.02**
16 weeks	**5(25)**	**17 (85)**	**0.0003**
ASAS 50 (n [%]) at:			
12 weeks	**2 (10)**	**11 (55)**	**0.01**
16weeks	**4 (20)**	**9 (45)**	**0.18**
ASAS 70 (n [%]) at:			
12 weeks	**0 (0)**	**2 (10)**	**0.49**
16 weeks	**3 (15)**	**5(25)**	**0.69**

* P-value determined by Fisher's exact test

Conversely, comparing the 50% responses of the pre-specified criteria in **(Table 55)** with the ASAS 50% values in **(Table 54),** the treatment difference is only statistically significant in the AS Response Criteria. The AS 50 Response Criteria and the ASAS Response Criteria achieve identical results in the 70% level for the etanercept group.

Table 55 Secondary Endpoints: AS 50/70% Response

Secondary Endpoint: Number (%) Achieving 50% and 70% Response Criteria			
	Placebo	**Etanercept**	**P-value**
50% Improvement	**N=20**	**N=20**	
Week 12	**2 (10)**	**14 (70)**	**0.01**
Week 16	**5 (25)**	**15 (75)**	**0.04**
70% Improvement			
Week 12	**2 (10)**	**2 (10)**	**1.00**
Week 16	**2 (10)**	**5 (25)**	**0.41**

* P-value determined by Fisher's exact test

Secondary Efficacy Analyses

In this study secondary analyses included: the individual components of the AS Response Criteria, Spinal Mobility Parameters, Physician Global Assessment, Pain Assessment, Delgados Spondylitis Functional Index (DSFI) and Krupp's Fatigue Measure. These will be discussed below.

Individual Components AS Response Criteria

The 5 components of the AS Response Criteria resemble the 4 domains recommended for assessment by of the ASAS Working Group. The major differences between the two systems are: 1) nocturnal back pain versus average of nocturnal back pain /total back pain in ASAS 2) intensity as well as duration of morning stiffness in ASAS and 3) the inclusion of swollen joints in the AS Response Criteria.

Etanercept recipients achieved statistically significantly greater improvement than placebo recipients as measured by 4 of the 5 components of the AS Response Criteria **(Table 56).** The component examining swollen peripheral joints demonstrated numerically higher response in etanercept recipients compared to placebo but this difference was not statistically significant. One possible explanation for the lack of response for swollen joints is the paucity of swollen joints in this disease.

Table 56 Secondary Endpoints: Individual Components of AS Response Criteria

Individual Components of AS Response Criteria

Mean (median) Values and Percent Improvement from Baseline					
	Mean (median) Values		Mean(median) Percent Improvement from Baseline		
	Placebo	Etanercept	Placebo	Etanercept	P-value
Parameter	N = 139	N = 138	N = 139	N = 138	
BASFI	Placebo	Etanercept	Placebo	Etanercept	
Baseline	63 (64)	63 (66)			
Week 12	56 (57)	35 (32)	10.5 (-4)	42.2 (-41)	0.01
Week 16	56 (57)	36 (29)	7.2 (7)	48.7 (-47)	0.0003
Nocturnal back pain †	Placebo	Etanercept	Placebo	Etanercept	P-value
Baseline	62 (65)	60 (62)			
Week 12	55 (56)	33 (26)	-2.8 (-11.6)	-55.5(-68)	0.0008
Week 16	56 (61)	34 (26)	-14.4 (-22)	-61.2 (-67)	0.001
Patient global assessment	Placebo	Etanercept	Placebo	Etanercept	P-value
Baseline	56 (59)	52 (50)			
Week 12	53 (53)	35 (29)	-7.1 (0.0)	-28 (-33)	0.01
Week 16	55 (55)	36 (31)	-11 (0.0)	-28 (-33)	0.02
Duration of morning stiffness	Placebo	Etanercept	Placebo	Etanercept	P-value
Baseline	64 (65)	61.4 (60)			
Week 12	53 (49)	32.8 (21)	(-17)	(-75)	0.01
Week 16	57 (58)	33.4 (26)	(-18)	(-76)	0.01
Swollen joint score					
Baseline	3.2 (1.0)	3.7 (0.0)			
Week 12	3.4 (0.5)	1.6 (0.0)	-8.4 (-38)	-74 (-77)	0.09
Week 16	3.7 (0.5)	1.6 (0.0)	-14 (0)	-47(-63)	0.3

Spinal Mobility Parameters

Assessments of spinal mobility utilized the same parameters as were used in both phase 3 studies. In this study, however, a statistically significant difference was demonstrated between etanercept and placebo at 16 weeks in two components and a strong trend for the third (the p-value of chest expansion was 0.0505 technically not statistically significant) **(Table 57).** At 12 weeks, only occiput to wall achieved statistical significance. It might be concluded from this data that receipt of etanercept is associated with statistically significant improvement in spinal mobility parameters when the measurements are taken 16 weeks into therapy but not necessarily at 12 weeks. Additionally, it would appear that chest expansion in this study was the least responsive.

Table 57 Other Endpoints: Spinal Mobility Parameters

Spinal Mobility Mean (Median) Values and Percent Change Baseline to Week 16					
	Actual Values		% change from baseline		
	Placebo	Etanercept	Placebo	Etanercept	
Parameter	n = 20	n = 20	n = 20	n = 20	P-value*
Chest expansion †					
Baseline	3.0 (3.1)	2.9 (2.6)	-	-	
Week 12	3.1 (3.0)	3.8 (4.0)	12.4 (0.0)	66.9 (20.0)	0.0994
Week 16	3.0 (2.9)	3.6 (3.5)	6.0 (0.0)	36.6 (22.5)	0.0505
Modified Schober's test					
Baseline	3.3 (3.5)	2.5 (2.5)	-	-	
Week 12	3.2 (3.5)	2.7 (2.8)	-4.0 (0.0)	15.8 (16.7)	0.0578
Week 16	3.2 (3.4)	2.8 (3.4)	-5.6 (-2.4)	21.1 (14.2)	0.0416
Occiput-to-wall measurement					
Baseline	2.0 (0.0)	5.7 (0.0)	-	-	
Week 12	2.1 (0.0)	4.9 (0.0)	16.7 (8.3)	-14.5 (-6.3)	0.0634
Week 16	2.7 (0.0)	4.7 (0.0)	84.1 (27.3)	-30.5 (-25.0)	0.0108

Physician Global Assessments

The Physician Global Assessments done in this study indicated that etanercept recipients had greater improvement from baseline than did placebo. This treatment difference was statistically significant **(Table 58).**

Table 58 Other Endpoints: Physician Global Assessment

Physician Global Assessment: Mean (Median) Values % Change From Baseline to Week 16						
		Actual values		% change from baseline		
		Placebo	Etanercept	Placebo	Etanercept	
Parameter		n = 20	n = 20	n = 20	n = 20	P-value*
Physician global assessment						
	Baseline	51.1 (48.0)	56.6 (54.5)	-	-	-
	Week 12	52.1 (59.0)	27.5 (30.0)	3.3 (0.0)	-53.8 (-58.2)	<0.0001
	Week 16	52.3 (55.5)	26.2 (23.0)	-0.7 (4.8)	-55.7 (-66.7)	<0.0001

Pain Assessment, Dougados Spondylitis Functional Index and Krupp's Fatigue Measure

The remaining three instruments have been published in the medical literature as useful in the measurement of Ankylosing Spondylitis disease activity and response to treatment **(Table 69 and 70 Appendices J and K)**. In this study, these instruments were used in the secondary endpoint analysis to assess their performance. As shown in **(Table 59)**, in each of the three instruments, etanercept achieved statistically higher response compared to placebo.

Table 59 Other Endpoints: Pain Assessment, DSFI, Krupp's Fatigue Measure

Pain Assessment, DSFI, Krupp's Fatigue Measure: Mean (Median) Values and Percent Change From Baseline to Week 16						
		Actual values		% change from baseline		
Parameter		Placebo n = 20	Etanercept n = 20	Placebo n = 20	Etanercept n = 20	P-value*
Pain						
	Baseline	49.6 (49.0)	58.3 (62.0)			
	Week 12	45.2 (53.5)	32.4 (29.5)	-2.8 (-11.9)	-42.4 (-44.4)	0.0066
	Week 16	43.6 (39.5)	32.5 (23.5)	-11.2 (-6.9)	-42.5 (-52.6)	0.0114
DSFI						
	Baseline	13.1 (12.0)	16.6 (18.0)			
	Week 12	11.6 (9.5)	11.7 (10.5)	-10.3 (-4.2)	-27.0 (-35.6)	0.1594
	Week 16	12.0 (10.0)	9.9 (8.0)	-3.9 (0.0)	-37.5 (-46.7)	0.0360
Krupp's fatigue measure						
	Baseline	4.3 (4.6)	4.6 (5.0)			
	Week 12	4.1 (3.7)	4.1 (4.2)	-1.3 (-6.0)	-5.2 (-15.0)	0.1478
	Week 16	4.5 (4.4)	4.0 (4.2)	8.2 (3.5)	-5.7 (-17.8)	0.0036

Conclusions

Efficacy

In study 016.0626, etanercept 25mg sc biw was statistically significant to placebo in achieving a 20% improvement in 3 of 5 pre-specified response criteria at 16 weeks. When ASAS Working Group Response Criteria are applied in ad hoc analysis, etanercept was statistically superior to placebo in the achievement of the ASAS 20 response at 16 weeks. Although the 50% response level achieves statistical significance using the pre-specified response criteria, neither the ASAS 50 nor the ASAS 70 achieves statistically significant improvement in this study. 4 of the 5 components of the pre-specified response criteria showed improvement, further supporting the superiority of etanercept over placebo. Swollen peripheral joint improvement while numerically higher in the etanercept recipients fails to reach statistical significance. In this 16-week study, all three spinal mobility parameters showed statistically significant improvement with etanercept compared to placebo. This study examined the performance of three additional instruments that have been published in the medical literature as useful in the measurement of Ankylosing Spondylitis disease activity and response to treatment.

The Spinal Pain Assessment, the Dougados Spondylitis Functional Index, and the Krupp's Fatigue Measurement independently indicated statistically significant improvement with etanercept.

Overall Summary of Efficacy

In all three studies that are reviewed in this document etanercept 25mg sc biw was superior to placebo in the achievement of pre-specified response criteria. For the two phase 3 studies, those pre-specified criteria were the ASAS Working Group Response Criteria. For the earlier phase 2 study, the pre-specified criteria were different but the result again demonstrated etanercept's superiority over placebo. In that phase 2 study, an ad hoc analysis using the ASAS Response Criteria, which were of necessity modified to accommodate those criteria, the results resemble those seen in the phase 3 studies.

Swollen peripheral joint assessment was one of the components of the phase response criteria for the 2 study and one in which etanercept superiority over placebo did not achieve statistical significance. Swollen and tender peripheral joint measurements were part of the other endpoints of the phase 3 studies. Only in study 016.0037 was statistically greater improvement demonstrated with etanercept and then only in tender joints but not swollen joints.

In all three studies, spinal mobility was a separately measured domain. The results of these measurements varied between studies with statistical significant improvement in all three components of spinal mobility seen in study 016.0037 but for only one component (modified Schober's test) in study 47687 and for two components in 016.0626. For the two studies with treatment beyond 12 weeks, the improvement in spinal mobility parameters appeared to increase with longer duration of etanercept treatment. The two studies that showed inconsistent results for the different measurements of spinal mobility were both smaller and of shorter duration than study 016.0037, where improvement was seen in all these measures.

Acute phase reactants were also separately measured in all three studies and in all three studies, ESR and CRP determinations supported greater improvement with etanercept than placebo.

Exploratory Analyses were performed on the largest of the three studies, study 016.0037. DCART 20 and DCART 40 that have been proposed as potentially useful in the assessment of short-term benefit in Ankylosing Spondylitis were performed and etanercept was demonstrated to be statistically superior to placebo in both. All subgroup analyses performed indicated that etanercept was superior to placebo although increasing age, female gender, being HLA-B27 negative and having concomitant psoriasis all appeared to be associated with lower response rates. The use of DMARDS did not appear to have an impact upon the treatment difference.

Overall Summary of Safety

In all three studies, injection site reactions and infections were consistently more common in the etanercept recipients versus the placebo recipients. The infections were mostly of Grade 1 and 2 intensity and infections of the upper airways and mouth appeared to be largely responsible for the higher incidence of infections in the etanercept recipients. In study 016.0037, a notable difference between safety withdrawals for etanercept and placebo were noted. Of the 7 safety withdrawals in that study, 4 were for bowel symptoms. Of the 4 withdrawals for bowel symptoms, 3 were for symptoms consistent with inflammatory bowel disease. Two of these were diagnosed as inflammatory bowel of which one represented a recurrence and the other a newly diagnosed inflammatory bowel disease. The significance of this is unknown.

Table 60 Appendix A Modified New York Criteria for Ankylosing Spondylitis

	Modified New York Criteria for Ankylosing Spondylitis
1.	Low-back pain of at least 3 months duration improved by exercise and not relieved by rest.
2.	Limitation of lumbar spine in sagittal and frontal planes.
3.	Chest expansion decreased relative to normal values for age and sex.
4.	Bilateral sacroiliitis, grade 2-4 (see Appendix J: Stoke).
5.	Unilateral sacroiliitis, grade 3-4 (see Appendix J: Stoke).
Definite AS if unilateral grade 3 or 4 or bilateral grade 2-4 sacroiliitis and any clinical criteria.	

Table 61 Appendix B : Stoke Ankylosing Spondylitis Spine Score

	Stoke Ankylosing Spondylitis Spine Score
0	Normal
1	Blurring of joint margin
2	1 + periarticular sclerosis or pseudo-widening
3	2 + erosions or partial bony bridging
4	Complete ankylosis

Table 62 APPENDIX C. BATH ANKYLOSING SPONDYLITIS FUNCTIONAL INDEX

Please draw a mark on each line below to indicate your level of ability with each of the following activities during the last week. (An aid is a piece of equipment which helps you to perform an action or movement.)

1) Putting on your socks or tights without help or aids (e.g. sock aid)
EASY_____ IMPOSSIBLE

2) Bending forward from the waist to pick up a pen from the floor without an aid
EASY _____ IMPOSSIBLE

3) Reaching up to a high shelf without help or aids (e.g. helping hand)
EASY_____ IMPOSSIBLE

4) Getting up out of an armless dining room chair without using your hands or any other help EASY_____ IMPOSSIBLE

5) Getting up off the floor without help from lying on your back
EASY_____ IMPOSSIBLE

6) Standing unsupported for 10 minutes without discomfort
EASY_____ IMPOSSIBLE

7) Climbing 12-15 steps without using a handrail or walking aid. One foot on each step
EASY_____ IMPOSSIBLE

8) Looking over your shoulder without turning your body
EASY_____ IMPOSSIBLE

9) Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports) EASY_____ IMPOSSIBLE

10) Doing a full day's activities whether it be at home or at work
EASY_____ IMPOSSIBLE

Table 63 APPENDIX D. BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX

Please place a mark on each line below to indicate your answer to each question, relating to the past week.

1) How would you describe the overall level of fatigue/tiredness you have experienced?

NONE_____ VERY SEVERE

2) How would describe the overall level of AS neck, back or hip pain you have had?

NONE _____VERY SEVERE

3) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

NONE_____ VERY SEVERE

4) How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

NONE_____ VERY SEVERE

5) How would you describe the overall level of morning stiffness you have had from the time you wake up?

NONE_____ VERY SEVERE

6) How long does your morning stiffness last from the time you wake up?

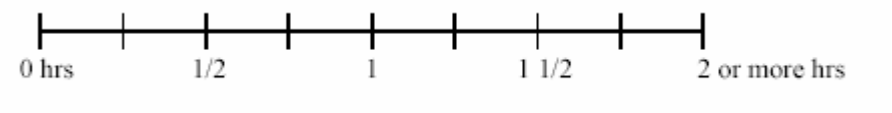


Table 64 **APPENDIX E. VISUAL ANALOG SCALE: PHYSICIAN GLOBAL ASSESSMENT**

Please place a vertical mark on the line below to indicate your overall assessment of the patient's disease activity during the last week.

NONE_____ SEVERE

Table 65 APPENDIX F. VISUAL ANALOG SCALE: PATIENT GLOBAL ASSESSMENT

Please place a vertical mark on the line below to indicate your overall assessment of your disease activity during the last week.

NONE_____ SEVERE

Table 66 APPENDIX G. VISUAL ANALOG SCALES: NOCTURNAL AND TOTAL BACK PAIN

Part A: Nocturnal Back Pain
Instructions: Based on your assessment, place one vertical line on the scale below from no pain to most severe pain.
What is the amount of back pain at night that you experienced during the last week?
NO PAIN_____ MOST SEVERE PAIN

Part B: Total Back Pain
Instructions: Based on your assessment, place one vertical line on the scale below from no pain to most severe pain.
What is the amount of back pain at any time that you experienced during the last week?
NO PAIN_____ MOST SEVERE PAIN

Table 67 APPENDIX H. PROCEDURES FOR SPINAL MOBILITY TESTING

1. Chest Expansion Score:
Measured circumferentially at nipple line in centimetres and recorded at maximal inspiration and maximal expiration. Record two tries, with the final score being the one with the larger difference between inspiration and expiration.
Inspiration (cm) Expiration (cm) Difference (cm)
First Try
Second Try

2. Schober's Test:
With the patient standing erect, place a mark in the midpoint of a line that joins the posterior superior iliac spines. Place another mark 10 cm above the first. Then, have the patient maximally bend forward, keeping the knees fully extended. With the spine in full flexion, remeasure the distance between the two marks in centimetres.

3. Occiput-to-Wall Measurement:
Place the patient standing with his/her back against the wall and measure the distance between the occiput and wall. The better (lesser distance) in centimetres will be recorded as the final value.
First Try: _____ Second Try: _____

Table 68 APPENDIX I. EVALUATION OF HIP INVOLVEMENT

R L
Does the patient have hip pain? Yes/No Yes/No
If yes: Medial/Lateral
Medial/Lateral
Does the patient have hip stiffness? Yes/No Yes/No
Is range of motion painful? Yes/No Yes/No
Is range of motion limited? Yes/No Yes/No
Does the patient have trochanteric tenderness? Yes/No Yes/No
Does the patient have antalgic gait? Yes/No Yes/No

Table 69 Appendix J Dougados Spondylitis Functional Index

Can You	Yes, with no difficulty (0)	Yes, but with difficulty (1)	No (2)
Put on your shoes			
Pull on trousers			
Pull on a pullover			
Get into a bathtub			
Remain standing for 10 minutes			
Climb 1 flight of stairs			
Run			
Sit down			
Get up from a chair			
Get into a car			
Bend over to pick up an object			
Crouch			
Lie down			
Turn in bed			
Get out of bed			
Sleep on your back			
Sleep on your stomach			
Do your job or housework			
Cough or sneeze			
Breath deeply			
Total Score			

Table 70 Appendix K Krupp Fatigue Severity Scale

Choose a number from 1 to 7 that indicates your degree of agreement with each of the following statements. One indicates strong **disagreement** and 7 indicates strong **agreement**.

1. My motivation is lower when I am fatigued.
2. Exercise brings on my fatigue.
3. I am easily fatigued.
4. Fatigue interferes with my physical functioning.
5. Fatigue causes frequent problems for me.
6. My fatigue prevents sustained physical functioning.
7. Fatigue interferes with carrying out certain duties and responsibilities.
8. Fatigue is among my three most disabling symptoms.
9. Fatigue interferes with my work, family, or social life.