24 June 2003 Arthritis Advisory Committee Meeting

Briefing Document for ENBREL® (etanercept)

For the Treatment of Ankylosing Spondylitis

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. Executive Summary

1.1 Background and Rationale

Ankylosing spondylitis (AS) is a chronic disease characterized by ankylosis of the spine, inflammation at the insertions of tendons, and occasionally peripheral arthritis. AS occurs predominantly in men, with onset before age 30, and produces pain and stiffness as a result of inflammation of the sacroiliac, intervertebral, and costovertebral joints. The disease afflicts approximately 350,000 patients in the United States (Carter et al, 1979).

The only approved therapies for AS are nonsteroidal anti-inflammatory agents (NSAIDs) (Toussirot and Wendling, 1998). These therapies reduce symptoms but have no demonstrated effect on the progressive, debilitating spinal immobility that is a hallmark of the disease. Second-line therapies, typically borrowed from the armamentarium for rheumatoid arthritis (RA), have demonstrated little effect or have been poorly studied. There is clearly a need for improved therapies for this disease.

There is accumulating evidence that tumor necrosis factor (TNF) plays an important role in AS, suggesting that anti-TNF therapies such as etanercept could offer benefits not provided by current therapies. The clinical data reviewed in this briefing package demonstrate that etanercept has the potential to be a significant therapeutic advance in the treatment of AS.

1.2 Clinical Development of Etanercept for the Treatment of Patients with Ankylosing Spondylitis

The AS clinical development program evaluated etanercept 25 mg twice weekly in 401 subjects in 3 randomized, double-blind, placebo-controlled studies. A proof-of-principle study evaluated etanercept in 40 AS subjects for 4 months. The results showed improvement in multiple parameters of disease activity, including spinal mobility measures (Gorman et al, 2002). Based on these data, Amgen initiated a 24-week study of 277 subjects with AS (Protocol 016.0037) and Wyeth initiated a similar 12-week study of 84 subjects (Study 0881A3-311-EU CSR 47687, hereafter referred to as Study 47687).

1.3 Summary of Efficacy

The efficacy of etanercept in subjects with AS is compelling. The positive findings in the proof-of-principle study were confirmed in a phase 3 study, Study 016.0037, where statistically significant responses for etanercept were seen as early as 2 weeks and

sustained at 12 and 24 weeks. The primary composite efficacy endpoint at week 12 was achieved by 60% of etanercept-treated patients compared with 27% of placebo patients ($p < 0.0001$). Sustained improvements were apparent in each component of the composite criteria, including inflammatory symptoms and patient physical function, and in measures of spinal mobility and acute phase reactants. The efficacy of etanercept in AS was again clearly demonstrated in a supportive study, Study 47687.

1.4 Summary of Safety

Etanercept was well tolerated by subjects with AS. Etanercept was associated with a higher incidence of injection site reactions, upper respiratory infections, and injury accidents than placebo. Few significant laboratory abnormalities were observed in these studies. Overall, the safety profile of etanercept in subjects with AS is similar to that observed in subjects with RA and psoriatic arthritis (PsA).

1.5 Conclusion

Three randomized, double-blind, placebo-controlled trials demonstrate that etanercept is effective in the treatment of subjects with AS, providing improvement in functional ability, spinal mobility, and acute-phase reactants. Etanercept is well tolerated in this patient population with a safety profile similar to that observed in etanercept clinical trials with other inflammatory rheumatic diseases. The risk benefit profile of etanercept in treating AS subjects is highly favorable. Based on these data, the following addition is proposed for inclusion in the etanercept product label:

> Etanercept is indicated for reducing signs and symptoms of active ankylosing spondylitis.

2. Rationale for Etanercept use in the Treatment of Ankylosing Spondylitis

2.1 Etanercept Background

Etanercept (ENBREL®) is a fully human dimer of 2 molecules of the extracellular portion of the p75 tumor necrosis factor receptor (TNFR) fused to the Fc portion of a type 1 human immunoglobulin (IgG1). Etanercept binds both TNF and lymphotoxin alpha (LTα) with high affinity.

Etanercept has been approved in the United States for reducing signs and symptoms and inhibiting the progression of structural damage in subjects with moderately to severely active RA; for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis (JRA) in subjects who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs); and for reducing signs and symptoms of active arthritis in subjects with psoriatic arthritis (PsA).

Etanercept has been administered to 3389 subjects in rheumatic disease clinical trials for currently approved indications and the postmarketing worldwide commercial experience with etanercept includes more than 180,000 patients. Clinical trials in RA have shown that etanercept remains safe and effective for over 6 years and allows subjects to reduce or discontinue the use of concomitant corticosteroids or methotrexate while maintaining clinical response.

2.2 Ankylosing Spondylitis

2.2.1 Description of the Disease Setting

Ankylosing spondylitis (AS) is a chronic inflammatory arthritis and enthesopathy involving the spine and peripheral joints. It occurs predominantly in men, with onset typically before age 30, and is associated with pain and stiffness resulting from inflammation of the sacroiliac, intervertebral, and costovertebral joints. It is one of the spondyloarthropathies (SpA) marked by absence of plasma rheumatoid factor and an association with HLA-B27. These diseases also include psoriatic arthritis (PsA), reactive arthritis (ReA), and arthritis associated with inflammatory bowel disease.

The prevalence of SpA is estimated to be 0.6% to 1.9% and is similar to the prevalence of RA (0.8%) (Braun and Sieper, 2002). It is estimated that there are currently over 350,000 AS patients in the United States (Carter et al, 1979).

A recent study showed that the degree of pain and disability among patients with AS is similar to that among patients with rheumatoid arthritis (Zink et al, 2000). Moreover, many patients with AS have severe inflammatory symptoms even decades after diagnosis of the disease (Ward, 1999; Gran and Skomsvoll, 1997; Kennedy et al, 1993; Goodacre et al, 1991; Ringsdal and Andreasen, 1989; Taylor et al, 1998).

2.2.2 Description of Currently Available Therapies

Traditional therapies, including NSAIDs, corticosteroids, and DMARDs, are inadequate for AS patients (Toussirot and Wendling, 1998). NSAIDs are often used for symptomatic relief but may not control disease activity and appear incapable of effecting the progressive spinal immobility that is characteristic of AS (Toussirot and Wendling, 1998). Sulfasalazine, while somewhat effective in treating peripheral arthritis, does little for axial disease (Dougados et al, 1995). A small controlled study of methotrexate demonstrated no effect on AS (Roychowdhury et al, 2001). In small studies, azathioprine showed some benefit in the treatment of ReA (Creemers et al, 1994). D-penicillamine, cyclophosphamide, levamisole, and methylprednisolone have yielded conflicting results (Creemers et al, 1994). Oral gold, corticotropin, or antimalarials are not effective in AS (Amor 1995; Creemers et al, 1994). Radiation treatment for synovitis has been abandoned because of its serious long-term side effects (Creemers et al, 1994). Treatment options for SpA are extremely limited.

2.2.3 Role of Tumor Necrosis Factor in Ankylosing Spondylitis

Tumor necrosis factor (TNF) plays a major role in the pathogenesis of AS. TNF levels are elevated in serum (Toussirot and Wendling, 1994, Gratacos 1994) and in synovial tissue (Canete et al, 1997; Grom et al, 1996) of patients with AS. These findings suggested that interfering with the pro-inflammatory effects of TNF could reduce the clinical signs and symptoms of AS and improve quality of life for patients with AS. As a result, Amgen initiated a clinical program to investigate the potential of etanercept as a new treatment for AS.

3. Development of Disease Response Criteria in Ankylosing Spondylitis

3.1 Ankylosing Spondylitis Assessment (ASAS) Working Group Criteria

AS is a systemic inflammatory disease that manifests variable clinical signs and symptoms. Assessment of patient status and response to treatment has been problematic. Since no disease-altering therapies were historically available, patients and

physicians learned to accommodate to progressive debility from AS by addressing the symptoms related to pain and inflammation. Definitive measures of AS had not been developed to assess the fundamental aspects of disease course.

To address the need for an effective clinical outcome measure optimal for studying new therapeutic agents, the Ankylosing Spondylitis Assessment (ASAS) Working Group was organized. This independent group of AS experts has been meeting for approximately 8 years, and their efforts toward establishing new AS assessment criteria have been published in peer-reviewed journals (Anderson et al, 2001; van der Heijde et al, 1999; van der Heijde et al, 1997).

After considering over 100 potential clinical outcome measures, ASAS identified a core set of 5 clinical domains considered essential for characterizing changes in AS: physical function, pain, spinal mobility, patient global assessment, and inflammation. Using data from clinical trials of NSAIDs in the treatment of AS to validate potential candidate response criteria from the 5 clinical domains, ASAS Working Group developed the Ankylosing Spondylitis Assessment Group Preliminary Definition of Short-Term Improvement in Ankylosing Spondylitis (ASAS 20), that included 4 of the 5 domains (Table 3-1 and Appendix 1) and specified instruments for measuring them. Spinal mobility was not included in the ASAS 20 because NSAIDs did not produce substantial improvement in spinal mobility in the validation trials and therefore the group did not consider it a good predictor of response. The ASAS 20 is modeled, at least in part, on composite outcome measures used in studies of rheumatoid arthritis and osteoarthritis (Anderson et al, 2001).

Table 3-1. Ankylosing Spondylitis Assessment Group Preliminary Definition of Short-Term Improvement in Ankylosing Spondylitis (Anderson et al, 2001)

An improvement of at least 20% and absolute improvement of at least 10 units on a scale of 0-100 in at least 3 of the following 4 domains: Patient global assessment is represented by the VAS global assessment score (0-100 scale) Pain is represented by the VAS pain score (0-100 scale) Function is represented by BASFI score (0-100 scale) Inflammation is represented either by (first choice) the mean of the 2 morning stiffness-related BASDAI VAS scores, or by (second choice) morning stiffness duration with a maximum of 120 minutes (0-100 scale). Absence of deterioration in the potential remaining domain, where deterioration is defined as a change for the worse of at least 20% and net worsening of at least 10 units on a scale of 0 to 100 VAS = visual analog scale

ASAS also defined a low level of disease activity as a "partial remission" of AS represented by a value of < 20 units (scale 1 to 100) in each of 4 domains of the ASAS 20 (Anderson et al, 2001). This endpoint was intended to provide a clinically meaningful definition of a low disease state independent of change or improvement in the ASAS 20.

3.2 Disease Controlling Anti-Rheumatic Therapy (DCART)

At a meeting convened October 30 to 31, 2002 to provide input for an FDA Guidance for disease-modifying therapies in AS, an advisory group including many members of the ASAS Working Group developed criteria for disease controlling anti-rheumatic therapy (DCART). Two composite response criteria were proposed.

The first, here called the DCART 20, combines the 4 criteria of the ASAS 20 with 2 additional criteria: improvement in spinal mobility and acute phase reactants. The DCART 20 requires a 20% improvement in 5 of the 6 criteria, with no worsening in the remaining criterion.

The second, hereafter called the DCART 40, requires a 40% improvement relative to baseline plus absolute improvement of at least 20 units in 3 of the 4 original ASAS 20 criteria, with no worsening in the remaining criterion. The DCART 40 is an alternative to the DCART 20 that considers different criteria (4 vs 6) and does not indicate a higher level of response than the DCART 20.

4. Description of the Etanercept Development Program for Ankylosing Spondylitis

4.1 Overview of the Program

The development program for etanercept in AS enrolled and treated 401 subjects with uncontrolled AS despite the use of NSAIDs and other therapies in 3 randomized, placebo-controlled studies. The first of these was Study 16.0626, a 4-month, proof-of-principle study in 40 subjects that demonstrated encouraging clinical response to etanercept (Gorman et al, 2002). With proof-of-principle established, 2 studies were initiated: Study 016.0037 (Amgen; N = 277 subjects), a 6-month study in the United States, France, Germany, and the Netherlands; and Study 0881A3-311-EU CSR 47687, hereafter referred to as Study 47687 (Wyeth; N = 84 subjects), a 3-month study in 8 European countries. These studies confirmed the safety and efficacy of etanercept in subjects with AS. Two open-label studies are ongoing and will allow for up to 2 years of continuous etanercept therapy.

4.2 Proof of Principle (Study 16.0626)

Study 16.0626 was a double-blind, proof-of-principle study that treated 40 subjects with AS (randomized 1:1) for 4 months with either etanercept (25 mg) or placebo twice weekly (BIW) and offered 6 months of open-label extension therapy. Inclusion criteria included: diagnosis of AS by modified New York Clinical Criteria (van der Linden 1984), presence of active disease (morning stiffness ≥ 45 minutes, inflammatory back pain, patient and physician global assessment of moderate or severe disease activity), and stable NSAIDs, steroids (≤ 10 mg of prednisone or equivalent) or DMARDs (methotrexate, sulfasalazine, azathioprine, 6-mercaptopurine). Subjects were not eligible if other forms of SpA were present, if they had received previous TNF inhibitor therapy, or if they were positive for rheumatoid factor.

Study 16.0626 was designed and conducted before the ASAS 20 was developed. The investigator prospectively defined response based on 5 clinical domains. The primary efficacy endpoint was the proportion of subjects in each group achieving a 20% improvement (compared with baseline) at week 16 in 3 of 5 response criteria (patient global assessment, nocturnal spinal pain, duration of morning stiffness, Bath Ankylosing Spondylitis Functional Index (BASFI), swollen joint score). For determination of efficacy, improvement in spinal pain or morning stiffness was required and worsening in the remaining 2 criteria was not permitted. The study also looked at multiple exploratory secondary endpoints.

The results of this study showed convincing efficacy for etanercept in the composite response criteria and its individual components (Table 4-1), as well as a reassuring safety profile with an absence of serious adverse events.

Table 4-1. Study 16.0626: Efficacy Results at Week 16

	Placebo n = 20	Etanercept n = 20	P-value [a]
Composite Response Criteria: number (%) achieving response			
Responders	5 (25)	15 (75)	0.0038 [b]
Individual components of composite response: mean (median) % improvement			
BASFI	-7.2 (-6.7)	48.7 (47.1)	0.0003
Nocturnal Back Pain	14.4 (21.5)	61.2 (66.7)	0.0014
Patient Global Assessment	10.8 (0.0)	28.0 (33.3)	0.0177
Duration of morning stiffness[c]	(18.3)	(76.4)	0.0116
	n = 11	n = 8	
Swollen Joint Score	14.2 (0.0)	46.9 (62.7)	0.2743

[a] Wilcoxon rank-sum test

[b] Fisher's exact test

[c] Mean % change is not represented as it is highly influenced by a small number of subjects

Significant improvement was also seen in some exploratory endpoints including total pain, joint pain/tenderness score, physician global assessment, Dougados Functional Index (DFI), Krupp's Fatigue Measure, modified Schober's Test, occiput-to-wall measurement, Westergren ESR, and the physical component summary score (PCS) of the SF-36.

Based on these results, the 2 larger studies were initiated.

4.3 Pivotal Program

4.3.1 Study Designs

Studies 016.0037 and 47687 were randomized, double-blind, placebo-controlled, phase 3 trials that randomized subjects in a 1:1 ratio (with stratification by baseline DMARD use) to receive etanercept (25 mg) or placebo BIW. In Study 016.0037, subjects were followed during 24 weeks of double-blind treatment, and in Study 47687, treatment and

observation was for 12 weeks. Subjects 18 to 70 years old were diagnosed with AS as defined by Modified New York Criteria for Ankylosing Spondylitis. They had active disease defined by values ≥ 30 on a 0 to 100 point VAS for duration/intensity of morning stiffness and 2 of the following 3 parameters: patient global assessment, average of VAS values for nocturnal back pain and total back pain, or average of 10 questions on the BASFI. Subjects were not allowed to enroll if they had clinical or radiographic evidence of complete ankylosis of the entire spine; had a history of active or recurrent infection; had ever received etanercept or other TNFα inhibitors; had received any investigational drug therapy within 30 days; had used DMARDs other than hydroxychloroquine, sulfasalazine, or methotrexate within 4 weeks of baseline evaluation; or had changed their dose of NSAIDs or prednisone (≤10 mg/ day or equivalent) within 2 weeks of baseline. Subjects were assessed for safety and efficacy at baseline and weeks 2, 4, 8, and 12 in both studies, and additionally at week 24 in Study 016.0037.

4.3.2 Study Endpoints

Efficacy

The pivotal program was developed before publication of the ASAS 20 (Anderson et al, 2001) and used an endpoint that differed slightly. The protocol-defined ASAS 20 used an average of total pain and nocturnal pain scores on the 100-mm visual analog scale (VAS) to represent the pain domain where the published ASAS 20 included only the total pain score. The difference in response criteria had no impact on the significance of the results.

The primary endpoint in both studies was the protocol-defined ASAS 20 criteria for response at week 12. The conditional primary endpoint in Study 016.0037, to be assessed if the primary endpoint was achieved, was the ASAS 20 response at week 24.

Other endpoints in both studies included frequency and time to partial remission, the individual components of the ASAS 20 (patient global assessment, nocturnal and total back pain, BASFI, and the average of duration and severity of morning stiffness from the Bath AS Disease Activity Index (BASDAI), the assessor global assessment, BASDAI, measurements of spinal mobility (the Schober test, measurement of chest expansion, and occiput-to-wall distance), peripheral joint counts, and laboratory assessment of inflammation (c-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]).

In addition to the ASAS 20 composite endpoints, the etanercept development program included assessments of higher levels of response based on the ASAS 20. The ASAS 50 and ASAS 70 are intended to parallel the use of higher levels of standard composite response criteria used in other rheumatic diseases. They are assessed identically to the ASAS 20 but require 50% and 70% improvement, respectively.

Responses were also assessed in Study 016.0037 with the DCART 20 and DCART 40. Further details on efficacy endpoints are in Appendix 1.

Safety

Safety evaluations in both studies included adverse events evaluated according to Common Toxicity Criteria, premature discontinuation, serious adverse events, deaths on study or within 30 days of last dose of study drug, vital signs and physical exams, hematology profile, chemistry profile, and anti-etanercept antibodies. See Appendix 1 for further details on safety endpoints.

4.4 Statistical Analyses

The statistical methods for analyzing efficacy and safety data were the same for Study 016.0037 and Study 47687 unless otherwise noted. Study 016.0037 and Study 47687 were analyzed using an intent-to-treat approach. All randomized subjects who received at least 1 dose of study medication were included in the analyses. All statistical tests were 2-sided and a significance level of 0.05 was used to declare statistical significance between treatment groups. No adjustments were made for multiple testing.

For binary efficacy endpoints, such as the ASAS 20, 50, and 70, and partial remission, subjects who discontinued from the study were declared nonresponders at all timepoints subsequent to their withdrawal. The Cochran-Mantel-Haenszel test (as given by the row means test in PROC FREQ from SAS), stratified by presence or absence of concomitant DMARDs at baseline, was used to compare response percentages between treatment groups.

For continuous efficacy endpoints, such as individual components of the ASAS 20, change and percent change from baseline were 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. Baseline was considered to be the last observation before the first dose of the study. Change and percent change from

baseline were computed for each endpoint such that a value greater than zero reflects improvement unless otherwise noted. Change and percent change were measured at the subject level and then summarized. Subjects with a zero score at baseline were not included in the analysis of percent improvement for the variable in question. A last-observation-carried-forward (LOCF) approach was used to impute missing data.

Safety endpoints: Treatment groups were compared with respect to incidence of adverse events and infections using Fisher's exact test for both studies unless otherwise noted.

5. Results for Pivotal Program

5.1 Study Populations

5.1.1 Baseline Demographics and Disease Characteristics

The treatment groups were well balanced within studies and were similar across studies with regard to demographic characteristics and baseline DMARDs (Table 5-1) and baseline disease characteristics (Table 5-2).

Table 5-1. Baseline Demographics and Therapy in the Pivotal Program

	Study 016.0037		Study 47687	
	Placebo	Etanercept	Placebo	Etanercept
Baseline characteristic	(N = 139)	(N = 138)	(N = 39)	(N = 45)
Mean age, yrs (range)	41.9 (18 – 65)	42.1 (24 – 70)	40.7 (19 – 66)	45.3 (28 – 63)
Men, n (%)	105 (76)	105 (76)	30 (77)	36 (80)
Mean duration of disease (years)	10.5	10.1	9.7	15.0
Mean weight (kg)	83.1	82.2	73.7	76.1
Race, n (%):				
White	127 (91)	130 (94)	37 (95)	42 (93)
Other	12 (8)	8 (6)	2 (5)	3 (7)
Baseline therapy, n (%):				
Any DMARD [a,b]	43 (31)	44 (32)	16 (41)	16 (36)
Sulfasalazine	30 (22)	29 (21)	11 (28)	11 (24)
Methotrexate	17 (12)	15 (11)	5 (13)	6 (13)
Hydroxychloroquine	1 (1)	3 (2)	1 (3)	0
NSAIDs [c]	128 (92)	126 (91)	33 (85)	40 (89)
Corticosteroids [c]	20 (14)	18 (13)	6 (15)	7 (16)

[a] Baseline therapies continued throughout trial.

[b] Some subjects were taking more than one DMARD.

[c] Concomitant NSAIDS or corticosteroids taken within 6 months of screening evaluation.

Table 5-2. Baseline Disease Characteristics in the Pivotal Program

	Study 016.0037		Study 47687	
	Placebo	Etanercept	Placebo	Etanercept
Baseline characteristic	(N = 139)	(N = 138)	(N = 39)	(N = 45)
Mean duration of AS, years (range)	10.5 (0 – 35.3)	10.1 (0 – 30.7)	9.7 (0.4 – 29.6)	15.0 (0.2 – 37.3)
Extra-spinal disease manifestations, n (%):				
History of Crohn's or ulcerative colitis	6 (4)	7 (5)	2 (5)	3 (7)
History of uveitis or iritis	43 (31)	39 (28)	6 (15)	13 (29)
History of psoriasis	15 (11)	11 (8)	3 (8)	10 (22)
HLA-B27 positive, n (%)	109 (84)	108 (84)	34 (87)	38 (88) [a]
ASAS 20 [b] components, mean (range):				
Patient global assessment	62.9 (9–100)	62.9 (16–100)	63.4 (31-86)	65.6 (26-100)
Total back pain	63.5 (0–99)	61.1 (7–100)	56.5 (22-86)	61.9 (22–100)
BASFI [c]	56.3 (11.5–97.0)	51.7 (4.3–97.7)	57.2 (18.5–82.4)	60.2 (13.9-100)
Stiffness, duration and intensity	64.3 (7–100)	61.4 (17–100)	62.9 (22–99.5)	67.5 (28-100)
Spinal mobility measures, mean (SE):				
Modified Schober's score[c], cm	2.97 (0.13)	3.06 (0.15)	2.8 (0.22)	2.2 (0.19)
Chest expansion, cm	3.21 (0.15)	3.26 (0.19)	3.9 (0.35)	3.3 (0.27)
Occiput-to-wall, cm	5.33 (0.56)	5.59 (0.50)	4.6 (0.85)	7.3 (0.92)
BASDAI[c], mean (SE)	59.6 (1.4)	58.1 (1.5)	58.6 (13.2) [d]	61.0 (15.7) [d]
Acute phase reactants, mean (SE):				
CRP (mg/dL) [e]	2.0 (0.2)	1.9 (0.2)	2.4 (4.2) [d]	1.9 (1.6) [d]
ESR (mm/hr) [f]	25.4 (1.9)	25.9 (1.8)	33.1 (23.9) [d]	30.6 (22.3) [d]

[a] Not assessed for 2 etanercept subjects

[b] See Appendix 1 for ASAS 20

[c] See Appendix 1, section 3

[d] Mean (standard deviation)

[e] Normal range 0 to 1.0 mg/dL.

[f] Normal range 1 to 17 mm/hr (men), 1 to 25 mm/hr (women)

5.1.2 Study Completion

Completion rates for Study 016.0037 at the 12-week (primary) time point was 96% placebo (134) and 96% etanercept (132). Completion rates at week 24 in this study were 86% placebo (120) and 91% etanercept (126). Reasons for premature withdrawal in Study 016.0037 included adverse events (7 etanercept subjects, 1 placebo), lack of efficacy (3 etanercept, 13 placebo), lost to follow-up (2 etanercept, 1 placebo), voluntary withdrawal (2 placebo), and lack of compliance with protocol (2 placebo).

In Study 47687, 84 subjects were enrolled; 2 subjects in the etanercept group withdrew from study for nonmedical reasons unrelated to safety.

5.2 Efficacy Results

5.2.1 Primary Endpoint: Protocol-Defined ASAS Response

Substantial etanercept-related improvement was evident in the results of the primary endpoint, the protocol-defined ASAS 20, as well as in the protocol-defined ASAS 50, protocol-defined ASAS 70, and partial remission criteria in Study 016.0037 at both the primary (week 12) and conditional primary (week 24) time points (Figure 5-1). Almost half the subjects in the study achieved and maintained a protocol-defined ASAS 50, and almost a third achieved a protocol-defined ASAS 70. Superior response was evident for etanercept-treated subjects at all levels of the protocol-defined ASAS score by week 2 and was maintained throughout the study ($p < 0.01$ at all visits). Seventeen percent of etanercept-treated subjects achieved partial remission at week 24 compared with 4% in the placebo group, and etanercept subjects achieved it faster than subjects in the placebo group (log-rank p-value < 0.0001).

Results in Table 5-3 are presented using both the protocol-defined ASAS 20 (see Section 4.3.2) and the ASAS 20 (per Anderson et al, 2001). Results for both analyses were similar.

The number of subjects receiving concomitant DMARDs were 44 (etanercept) and 43 (placebo). The responses were similar in etanercept subjects with or without concomitant DMARDs, 61% and 60%, respectively.

Secondary endpoints are presented in Table 5-4.

The magnitude and time course of etanercept-related improvement was similar in Study 47687 (Table 5-5), but did not achieve statistical significance for all secondary endpoints, possibly due to the smaller sample size.

Table 5-3. Study 016.0037: Primary Endpoint: ASAS 20 at Weeks 12 and 24

	Protocol-Defined ASAS 20 [a]			ASAS 20 [b]		
Parameter	Placebo N = 139	Etanercept N = 138	P-value [c]	Placebo N=139	Etanercept N=138	P-value [c]
ASAS 20 (n/%)						
12 weeks	38 (27)	83 (60)	< 0.0001	39 (28)	82 (59)	<0.0001
24 weeks	32 (23)	80 (58)	< 0.0001	31 (22)	78 (57)	<0.0001

[a] Protocol-defined ASAS 20 is calculated with average of total and nocturnal back pain

[b] ASAS 20 is calculated using only total back pain (Anderson et al, 2001)

[c] Cochran-Mantel-Haenszel row means test

Table 5-4. Study 016.0037: Secondary Endpoints: ASAS 50 and 70, and Partial Remission at Weeks 12 and 24

	Protocol-Defined ASAS 20 [a]		
Parameter	Placebo N = 139	Etanercept N = 138	P-value [b]
ASAS 50 (n/%)			
12 weeks	18 (13)	62 (45)	< 0.0001
24 weeks	14 (10)	58 (42)	< 0.0001
ASAS 70 (n/%)			
12 weeks	10 (7)	40 (29)	< 0.0001
24 weeks	7 (5)	39 (28)	< 0.0001
Partial Remission (n/%)			
12 weeks	11 (8)	29 (21)	0.0020
24 weeks	5 (4)	24 (17)	0.0002

[a] Protocol-defined ASAS 20 is calculated with average of total and nocturnal back pain

[b] Cochran-Mantel-Haenszel row means test

Figure 5-1. Study 016.0037: Percent of Subjects Achieving Protocol-Defined ASAS 20, 50, and 70 Over Time

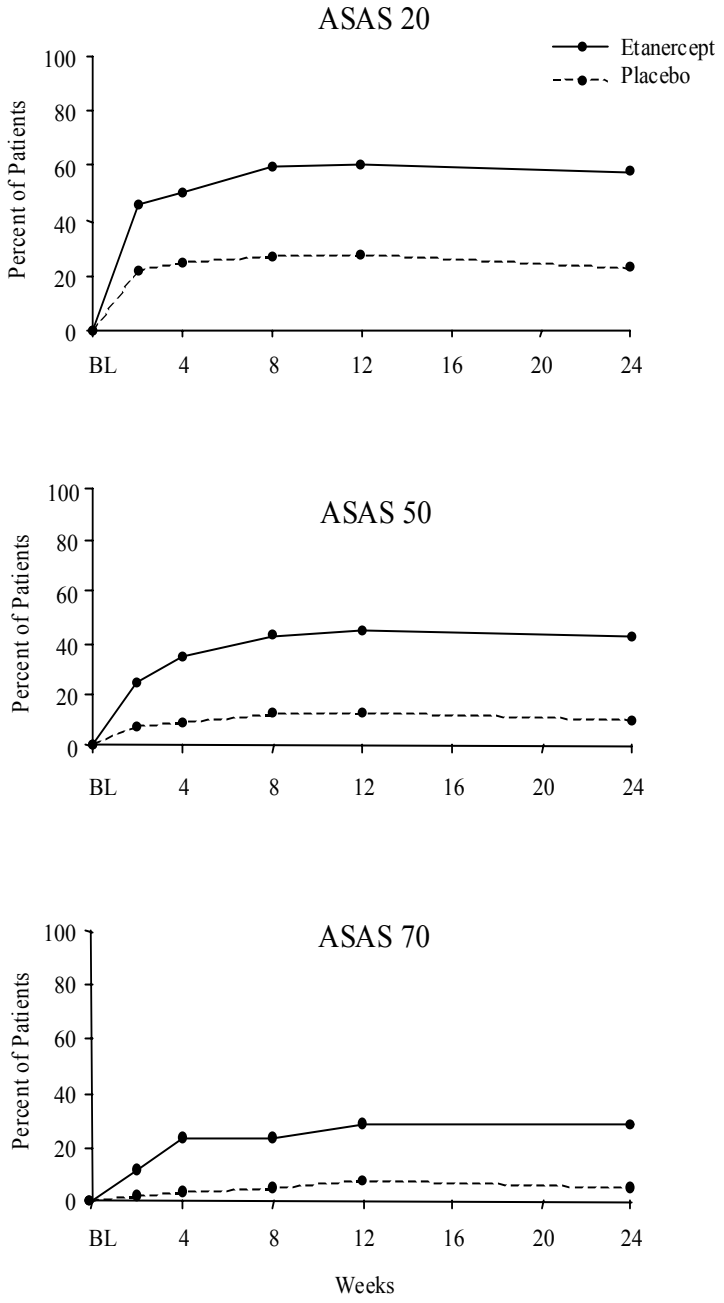

Table 5-5. Study 47687. Primary and Secondary Endpoints: ASAS 20, 50, 70, and Partial Remission at Week 12

Parameter	Placebo N = 39	Etanercept N = 45	P-value [a]
ASAS 20 (n/%)	9 (23)	27 (60)	0.0008
ASAS 50 (n/%)	4 (10)	22 (49)	0.0002
ASAS 70 (n/%)	4 (10)	11 (24)	0.0973
Partial Remission (n/%)	4 (10)	8 (18)	0.3457

[a] Cochran-Mantel-Haenszel row means test

5.2.2 Individual Components of ASAS 20

All components of the ASAS 20 reflected substantial etanercept-related improvement at both primary time points (Table 5-6) and at all other time points measured ($p < 0.0005$) in Study 016.0037, indicating that etanercept acts on a broad range of disease symptoms. The median percent improvement in pain was approximately 10-fold higher with etanercept than with placebo, with an apparent advantage in the other component scores. Comparable efficacy was observed in Study 47687 (Table 5-7).

Table 5-6. Study 016.0037: Results for Individual Components of Protocol-Defined ASAS 20

Parameter	Mean (median) Percent Improvement from Baseline		
	Placebo N = 139	Etanercept N = 138	P-value [b]
Patient Global Assessment			
12 weeks	9.8 (8.8)	40.2 (50.8)	< 0.0001
24 weeks	7.8 (6.5)	38.6 (46.3)	< 0.0001
Avg nocturnal back pain and total back pain[a]			
12 weeks	6.7 (5.4)	39.9 (54.1)	< 0.0001
24 weeks	5.1 (6.0)	34.8 (51.1)	< 0.0001
BASFI – average of responses to 10 questions			
12 weeks	4.9 (3.3)	33.1 (32.3)	< 0.0001
24 weeks	1.9 (-1.0)	30.1 (31.3)	< 0.0001
Inflammation (BASDAI)			
12 weeks	13.1 (9.5)	44.8 (55.1)	< 0.0001
24 weeks	5.7 (5.0)	43.9 (45.0)	< 0.0001

[a] One subject in the placebo group had a score of zero at baseline for the average nocturnal back pain and total back pain and was not included in the analysis of percent improvement from baseline for that measure

[b] Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline

Table 5-7. Study 47687: Results for Individual Components of the Protocol-Defined ASAS 20 at Week 12

Parameter	Mean Percent Improvement from Baseline		
	Placebo N = 39	Etanercept N = 45	P-value [a]
Patient Global Assessment	12.6	37.0	0.0107
Avg nocturnal back pain and total back pain	6.2	43.1	0.0003
BASFI – average of responses to 10 questions	3.4	35.4	0.0003
Inflammation (Average of last 2 questions on BASDAI related to morning stiffness)	15.9	43.3	0.0025

[a] Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

5.2.3 Additional Measures of Disease Activity

Etanercept therapy was associated with substantial improvement in a number of endpoints not included in the ASAS 20. Measures of spinal mobility were excluded from the composite criteria because they showed no change in response to NSAID therapy. Etanercept treatment was associated with significantly more improvement in all 3 measures of spinal mobility than placebo in Study 016.0037 (Table 5-8), with median percent improvement ranging from 10% to 25% across measures at week 24 compared with 0% in the placebo group.

Median percent improvement for the indicators of disease activity and inflammation (BASDAI, acute phase reactants) ranged from 40% to 73% in the etanercept group at weeks 12 and 24 and was superior to placebo at every study visit ($p < 0.0001$). In the etanercept group, the percent of subjects with normal (nonelevated) acute phase reactants increased from 46% for both reactants at baseline to 83% ESR, 85% CRP at week 24, while in the placebo group they remained unchanged.

Independent assessors judged global disease to be significantly improved in the etanercept group vs placebo at every study visit ($p < 0.01$), with median percent improvement of 45% at weeks 12 and 24, more than 3-fold higher than with placebo (approximately 13% at both time points).

Tender joint counts improved with etanercept therapy but not swollen joint counts. The lack of significant treatment effect on swollen joint counts was likely due to the small number of subjects with peripheral joints involved and the small number of joint counts involved in each subject (median swollen joint count at baseline: placebo, 0; etanercept, 1).

Similar improvement was seen in Study 47687 (Table 5-9), although mean percent improvement in joint counts were not available.

Table 5-8. Study 016.0037: Results for BASDAI, Spinal Mobility, Acute Phase Reactants, Assessor Global, and Peripheral Joint Counts.

Parameter	Mean (median) Percent Improvement from Baseline [a] Placebo N = 139	Etanercept N = 138	P-value [b]
BASDAI			
12 weeks	11.3 (9.9)	42.2 (44.6)	< 0.0001
24 weeks	5.8 (3.1)	39.5 (40.4)	< 0.0001
Spinal Mobility Measures			
Schober's Test			
12 weeks	21.4 (0)	25.6 (8.6)	0.0359
24 weeks	7.8 (0)	25.1 (9.7)	0.0014
Chest Expansion			
12 weeks	11.2 (0)	57.8 (4.8)	0.0026
24 weeks	-0.6 (0)	56.5 (16.7)	< 0.0001
Occiput-to-Wall Measurements			
12 weeks	-80.9 (0)	18.3 (15.7)	0.0034
24 weeks	-98.7 (0)	26.0 (25.0)	< 0.0001
Acute Phase Reactants			
ESR (mm/hr)			
12 weeks	-19.2 (0)	17.7 (60.0)	< 0.0001
24 weeks	-23.0 (0)	42.1 (60.0)	< 0.0001
C-reactive Protein (mg/dL)			
12 weeks	-142.5 (-5.4)	10.1 (68.5)	< 0.0001
24 weeks	-95.9 (0)	38.0 (72.7)	< 0.0001
Assessor Global			
12 weeks	10.3 (13.5)	34.2 (45.0)	< 0.0001
24 weeks	5.9 (13.2)	29.5 (45.2)	< 0.0001
Tender Joint Count	n=114	n=101	
12 weeks	-1.0 (20.6)	36.8 (50.0)	0.0061
24 weeks	1.4 (31.4)	35.5 (61.5)	0.0014
Swollen Joint Count	n=65	n=73	
12 weeks	-14.6 (50.0)	35.7 (66.7)	0.1263
24 weeks	-10.5 (50.0)	3.7 (60.0)	0.8384

[a] Subjects with a score of zero at baseline were not included in the analysis of percent improvement from baseline for that measure

[b] Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

Table 5-9. Study 47687: Results for BASDAI, Spinal Mobility, Acute Phase Reactants, and Assessor Global at Week 12

	Mean Percent Improvement from Baseline [a]		
Parameter	Placebo N = 39	Etanercept N = 45	P-value [b]
BASDAI	13.6	43.6	0.0014
Spinal Mobility Measures			
Schober's Test	-1.3	36.0	0.0085
Chest Expansion	9.0	29.9	0.8695
Occiput to Wall Measurements	7.2	12.5	0.0650
Acute Phase Reactants			
ESR (mm/hr)	0.0	79.6	0.0000
C-reactive Protein (mg/dL)	0.0	69.5	0.0000
Assessor Global	19.8	39.3	0.0321

[a] Subjects with a score of zero at baseline were not included in the analysis of percent improvement from baseline for that measure

[b] Cochran-Mantel-Haenszel row means test with Modridit option on percent improvement from baseline.

5.2.4 Disease-Controlling Anti-Rheumatic Therapy Response

The DCART 20 and DCART 40 response criteria are discussed in Section 3.2 and are defined in Appendix 1.

The proportion of subjects who attained the DCART responses was more than 3-fold higher with etanercept therapy than with placebo at week 24 (Table 5-10). Statistically significant improvements were evident at all time points during the study compared with the placebo group (data on file).

Table 5-10. Study 016.0037: DCART 20 and DCART 40 Responses

	Placebo N = 139	Etanercept N = 138	P-value*
DCART 20 (n/%)			
12 weeks	11 (8)	51 (37)	< 0.0001
24 weeks	10 (7)	46 (33)	< 0.0001
DCART 40 (n/%)			
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.

5.2.5 Subgroup Analyses for Study 016.0037

Exploratory analyses were conducted to evaluate the primary endpoint within subgroups defined by baseline demographics (including age, sex, weight, race, HLA-B27, study site, prior use of NSAIDS or corticosteroids, or concomitant DMARD use), baseline disease status (patient global score; average of nocturnal back pain and total back pain; inflammation; BASFI; BASDAI; disease duration; history of extraspinal and extra-articular involvement; hip disease), and occurrence of injection site reactions during the study. These analyses should be interpreted with caution. No adjustments for multiple analyses were performed.

The following subgroup variables had significant treatment-by-subgroup interaction p-values ($p<0.05$): HLA-B27 status, baseline average of nocturnal back pain and total back pain (above and below median), and baseline BASDAI (above and below median).

In subjects with a positive HLA-B27 test (etanercept, n=108; placebo, n=109), ASAS 20 responses (etanercept, 65%; placebo, 27%) were comparable to the overall study results. In subjects with a negative HLA-B27 test (etanercept, n=21; placebo, n=20), the week-12 results showed that ASAS 20 was achieved by a similar percentage of subjects in both the etanercept group (38%) and the placebo group (35%). By week 24, however, a treatment advantage was apparent in ASAS 20 response for etanercept (48% of subjects) vs placebo (20%) among HLA-B27-negative subjects. The relevance of this finding is unclear, but the relatively small number of HLA-B27-negative subjects may have contributed to this outcome.

For average back pain at week 12, the ASAS 20 responses for the etanercept subgroup compared with the placebo subgroup were 54% vs 34% for subjects with ≤ median back pain and were 67% vs 22% for subjects with > median back pain. In both subgroups, the etanercept subjects had significantly higher responses than the placebo subjects. Similarly, ASAS 20 responses for etanercept compared with placebo were significantly higher in both BASDAI subgroups (56% vs 36% and 65% vs 19% grouped as ≤ median and > median for BASDAI, respectively). Neither of the subgroup analyses for back pain or BASDAI suggests a different conclusion regarding the efficacy of etanercept compared with placebo with respect to the primary endpoint.

5.3 Summary of Efficacy Results

Three randomized, double-blind, placebo-controlled clinical trials demonstrated marked efficacy of etanercept in the treatment of AS. A proof-of-principle trial demonstrated clinical response in its prespecified clinical composite measure as well as in most of the individual response measures used. Two additional studies, a 277-subject study performed by Amgen (Study 016.0037) and an 84-subject study performed by Wyeth (Study 47687), confirmed the effectiveness of etanercept in treatment of AS. The primary endpoint in both studies was the proportion of subjects achieving a composite endpoint, the protocol-defined ASAS 20, at 12 weeks.

In study 016.0037, a significantly greater proportion of etanercept-treated subjects (60%) than placebo subjects (27%) met the protocol-defined ASAS 20 at 12 weeks ($p < 0.0001$). Since the primary endpoint was significantly greater in the etanercept group, a conditional primary endpoint (protocol-defined ASAS 20 at 24 weeks) was to be evaluated. The results at 24 weeks were similar to those at 12 weeks with 58% and 23% of subjects achieving the protocol-defined ASAS 20 in the etanercept and placebo groups, respectively. Additional composite measures were also evaluated: protocol-defined ASAS 50 and ASAS 70, partial remission, DCART 20, and DCART 40. Each one of these endpoints was achieved by a significantly greater proportion of subjects in the etanercept group compared with the placebo group at all time points measured (weeks 2, 4, 8, 12, and 24).

The results of the Study 016.0037 are supported by the results of Study 47687. A significantly greater proportion of etanercept-treated subjects (60%) achieved a protocol-defined ASAS 20 compared with 23% of placebo subjects. Response rates for higher levels of protocol-defined ASAS 20 were also supportive of Study 016.0037.

Study 47687 supports the conclusions of Study 016.0037 with comparable results. Etanercept provides clinically and statistically meaningful benefit to subjects with AS.

6. Safety Results

6.1 Overview of Safety Results

The adverse events profiles seen in Studies 016.0037 and 47687 are summarized in Table 6-1. The overall incidence of adverse events was not increased by etanercept in any study, and no deaths were seen. Etanercept was associated with a higher incidence of injection site reactions. These findings are further described in the sections that follow.

Table 6-1. Overall Summary of Adverse Events in Studies 016.0037 and 47687: Number (%) of Subjects Reporting Adverse Events

	Study 016.0037		Study 47687	
	Placebo N = 139	Etanercept N = 138	Placebo N = 39	Etanercept N = 45
Serious adverse events	5 (3.6)	9 (6.5)	0 (0)	1 (2.2)
Medically important infections[a]	1 (0.7)	2 (1.4)	0 (0)	0 (0)
Events leading to withdrawal	1 (0.7)	7 (5.1)	0 (0)	0 (0)
Non-infectious adverse events[b]	105 (76)	99 (72)	23 (59.0)	25 (55.6)
Injection site reactions	13 (9)	41 (30)[c]	6 (15)	15 (33)[d]
Infections	42 (30)	57 (41)	13 (33.3)	16 (35.6)

ISR = injection site reaction

[a] Infections requiring hospitalization or parenteral antibiotics

[b] Excluding infections and injection site reactions

[c] P < 0.0001, Fisher's exact test

[d] P = 0.0283, Cochran-Mantel-Haenszel row means test

6.2 Serious Adverse Events

No deaths were reported in any of the studies of etanercept in subjects with AS. A total of 10 of 183 etanercept-treated subjects (5%) had serious adverse events.

In Study 016.0037, the incidence of serious adverse events was not significantly different in the etanercept (9 subjects) and placebo (5 subjects) groups (Table 6-2). The only serious event ocurring in more than a single subject in the etanercept group was bone fracture. Three subjects sustained bone fracture secondary to trauma. All cases were considered unrelated to etanercept.

Table 6-2. Study 016.0037: Summary of Serious Adverse Events

	Placebo N = 139	Etanercept N = 138
Any (n/%)	5 (3.6)	9 (6.5)
Bone fracture (n/%)	0 (0.0)	3 (2.2)
Accidental injury (n/%)	2 (1.4)	0 (0.0)
Cellulitis (n/%)	0 (0.0)	1 (0.7)
Colitis (n/%)	0 (0.0)	1 (0.7)
Fever (n/%)	0 (0.0)	1 (0.7)
Infection (n/%)	0 (0.0)	1 (0.7)
Viral infection (n/%)	1 (0.7)	0 (0.0)
Lymphadenopathy (n/%)	0 (0.0)	1 (0.7)
Intestinal obstruction (n/%)	0 (0.0)	1 (0.7)
Chest pain (n/%)	1 (0.7)	0 (0.0)
Rash (n/%)	0 (0.0)	1 (0.7)
Suicide attempt (n/%)	1 (0.7)	0 (0.0)

In Study 47687, the only serious event was a myocardial infarction in the etanercept group. The event was considered unrelated to etanercept, therapy was continued, and the subject completed study.

6.3 Medically Important Infections

Medically important infections were those requiring hospitalization or treatment with intravenous (IV) antibiotics. Three events occurred in Study 016.0037. Two occurred in the etanercept group: an infection secondary to a cat bite and cellulitis secondary to an

insect bite. In the placebo group, one subject experienced a viral infection. No life-threatening infections occurred in Study 016.0037. No medically important infections occurred in Study 47687.

6.4 Withdrawals Because of Adverse Events

Withdrawals because of adverse events in Study 016.0037 are summarized in Table 6-3.

Table 6-3. Study 016.0037: Summary of Adverse Events Causing Withdrawal

	Placebo N = 139	Etanercept N = 138
All (n/%)	1 (0.7)	7 (5.1)
Bone fracture (n/%)	0 (0.0)	2 (1.4)
Fever (n/%)	0 (0.0)	1 (0.7)
Hemorrhoidal bleeding (n/%)	0 (0.0)	1 (0.7)
Ileitis (n/%)	0 (0.0)	1 (0.7)
Obstruction intestinal (n/%)	0 (0.0)	1 (0.7)
Ulcerative colitis (n/%)	0 (0.0)	1 (0.7)
Suicide attempt (n/%)	1 (0.7)	0 (0.0)

No withdrawals because of adverse events occurred in Study 47687.

6.5 Noninfectious Adverse Events

The incidence of the most common adverse events in each of the AS studies is shown in the following table by study. The overall incidence of adverse events was comparable in both etanercept and placebo groups in both studies, with the exception of injection site reactions and injury accidents.

Other than injection site reactions, discussed in Section 6.1, the only noninfectious adverse event that occurred significantly more frequently in the etanercept group was accidental injury in Study 016.0037 (Table 6-4). Most adverse events were of mild or moderate intensity. The only life-threatening event was an attempted suicide in the placebo group.

Eight subjects in the placebo group and 3 subjects in the etanercept group had flares of uveitis during the Study 016.0037. One subject in the placebo group and no subject in the etanercept group had flares of uveitis in Study 47687.

Three subjects experienced adverse events related to inflammatory bowel disease during Study 016.037. A subject in the etanercept group with a history of recurrent flares of ulcerative colitis requiring treatment with steroids had 2 flares during the study. Two subjects were diagnosed with Crohn's disease during the study, one in the placebo group and one in the etanercept group.

Table 6-4. Noninfectious Adverse Events in ≥ 5% of Subjects in Either Study or Treatment Group

	Study 016.0037		Study 47687	
	Placebo N = 139	Etanercept N = 138	Placebo N = 39	Etanercept N = 45
Any (n/%)	105 (76)	99 (72)	23 (59)	25 (56)
Injection site ecchymosis (n/%)	23 (17)	29 (21)	4 (10)	8 (18)
Headache (n/%)	16 (12)	19 (14)	4 (10)	6 (13)
Accidental injury (n/%)	6 (4)	17 (12)[a]	2 (5)	0
Diarrhea (n/%)	13 (9)	11 (8)	2 (5)	2 (4)
Rash (n/%)	9 (7)	11 (8)	0	2 (4)
Dizziness (n/%)	3 (2)	8 (6)	1 (3)	1 (2)
Rhinitis (n/%)	9 (7)	8 (6)	0	1 (2)
Abdominal pain (n/%)	7 (5)	8 (6)	2 (5)	1 (2)
Nausea (n/%)	7 (5)	7 (5)	4 (10)	3 (7)
Asthenia (n/%)	7 (5)	5 (4)	1 (3)	5 (11)

[a] $P < 0.05$ (Fisher's exact test)

6.6 Infections

Infections are summarized in Table 6-5. In Study 016.0037, upper respiratory infections were more common in the etanercept group than in the placebo group (20% vs 12%). This increase was not evident in Study 47687 (9% vs 8%). Most infections in Study

016.0037 were of mild or moderate intensity, and no life-threatening infections occurred. No opportunistic infections were observed in any study.

Table 6-5. Infections in ≥ 5% of Subjects in Either Study or Treatment Group

	Study 016.0037		Study 47687	
	Placebo N = 139	Etanercept N = 138	Placebo N = 39	Etanercept N = 45
Any (n/%)	42 (30)	57 (41)	13 (33.3)	16 (35.6)
Any infection except URI (n/%)	28 (20)	33 (24)	NA	NA
Upper respiratory infection (n/%)	16 (12)	28 (20) [a]	3 (7.7)	4 (8.9)
Flu syndrome (n/%)	10 (7)	5 (4)	2 (5.1)	1 (2.2)

NA = not available; URI = upper respiratory infection

[a] $P < 0.05$ (Fisher's exact test)

6.7 Malignancies

No malignancies were reported in any of the studies.

6.8 Clinical Laboratory Results

In Study 016.0037 and Study 47687, clinical laboratory results were categorized using a modified National Cancer Institute (NCI) common toxicity scale and the central laboratory's normal ranges for each parameter. Baseline clinical laboratory values for each subject was determined from blood and urine samples obtained before administration of study drug.

In Study 016.0037, 3 subjects in the etanercept group had transient grade 3 or 4 low absolute neutrophil counts (ANC) or lymphocyte counts. One subject, whose ANC at screening was normal, had grade 3 ($0.5x10^9$/L) low ANC at week 12. A repeat sample 6 days later was normal, although the subject had grade 1 ANC at the end-of-study evaluation. A second subject had persistent grade 2 low lymphocytes from screening through end-of-treatment, with a transient grade 3 result noted at the week-12 visit. Neither of these subjects experienced an infection during the study. One subject who had normal ANC at screening, had grade 4 low ANC at baseline and grade 1 low ANC for the duration of the study.

In Study 47687, 1 subject in the etanercept group had grade 3 abnormal values for aspartate aminotransferase, alanine aminotransferase, and bilirubin during therapy. This subject had increased transaminases and bilirubin serum values at the week-12 visit. The subject continued on open-label etanercept, and after 4 weeks liver function tests had normalized. No subjects in the placebo group had clinically important laboratory abnormalities.

No subject discontinued either study due to abnormal laboratory values.

6.9 Antibody Results

Testing for anti-etanercept antibodies was conducted in Studies 016.0037 and 47687.

In Study 016.0037, antibodies to etanercept were detected in samples from 3 subjects (2.2%) in the etanercept group. Serum samples from all 3 subjects were negative in a binding assay for neutralizing antibodies. All other serum samples were negative for anti-etanercept antibodies.

In Study 47687, all serum samples were negative for anti-etanercept antibodies.

6.10 Safety Summary and Conclusions

Etanercept was safe when administered to subjects with AS at a dose of 25 mg BIW for 24 weeks. No deaths occurred in any study. Most adverse events were of mild or moderate intensity. Nine subjects had 10 serious adverse events receiving etanercept, and 5 serious events occurred in 5 subjects receiving placebo. Seven subjects receiving etanercept and one receiving placebo discontinued study drug due to adverse events.

No life-threatening infections occurred during either study. Three infections occurred that required hospitalization or IV antibiotics, 2 in subjects receiving etanercept and 1 in a subject receiving placebo. In Study 016.0037, upper respiratory infections were significantly more frequent in subjects receiving etanercept. This difference was not observed in Study 47687. No opportunistic infections were observed.

Few abnormal laboratory results exceeded grade 2 intensity, and no subject was discontinued from study due to an abnormal laboratory result. Antibodies to etanercept were detected by ELISA in serum samples from 3 subjects; all samples were negative for neutralizing antibodies.

6.11 Safety Profile in Ankylosing Spondylitis is Comparable to Established Etanercept Safety Profile in Rheumatic Diseases

Etanercept has been the subject of extensive investigation and safety evaluations. The FDA and the Arthritis Advisory Committee have evaluated etanercept extensively on multiple occasions:

Year	Indication	Reviewed by:
1998	Approval for RA (alone or with MTX)	FDA, Arthritis Advisory Committee
1999	Approval for JRA	FDA
2000	Approval as initial therapy for RA/ Approval for inhibition of radiographic progression	FDA, Arthritis Advisory Committee
2001	FDA Arthritis Advisory re: TNF Antagonists Safety	FDA, Arthritis Advisory Committee
2002	Approval for psoriatic arthritis (alone or with MTX)	FDA
2002	Approval of 3-year efficacy and safety data in RA	FDA
2003	FDA Arthritis Advisory re: TNF Antagonists Safety	FDA, Arthritis Advisory Committee
2003	50-mg Dosing Regimen Once Weekly in RA	FDA review ongoing

MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumor necrosis factor

6.11.1 Clinical Trials in Subjects with Rheumatoid Arthritis and Psoriatic Arthritis

The etanercept clinical trial database through 2002 includes 3389 subjects who have received etanercept in Amgen- and Wyeth-sponsored rheumatic disease clinical trials for currently approved indications. In open-label extension studies, the efficacy and the safety profile associated with longer-term administration of etanercept (up to 6 years) remain stable over time.

In 3- to 6-month controlled clinical trials in rheumatic diseases, the only adverse event occurring more frequently in etanercept-treated subjects relative to placebo-treated subjects was injection site reactions.

Results from long-term, open-label studies show that adverse event rates do not increase with prolonged exposure to etanercept.

6.11.2 Comparison of Etanercept Safety Results in Ankylosing Spondylitis with Rheumatoid Arthritis and Psoriatic Arthritis Populations

The safety profile of etanercept in subjects with AS is compared with the profile observed in subjects with RA and PsA in Table 6-6 using adverse event rates adjusted

for total exposure to etanercept. Overall, the safety profile of etanercept in subjects with AS is comparable to that observed in subjects with RA and PsA.

Table 6-6. Exposure-adjusted Incidence (Events/Subject-Year) of Adverse Events and Infections in Controlled Studies of Etanercept in Subjects with RA, PsA, or AS

Event	Rheumatoid Arthritis			PsA	AS
	Protocol 016.0009 [a]	Protocol 016.0014 [b]	Protocol 016.0012 [c]	Protocol 016.0030 [d]	Protocol 016.0037
Any adverse event	4.58	5.02	5.94	3.28	6.10
Serious adverse event	0.15	0.11	0.09	0.14	0.17
Any infection	2.55	2.07	1.54	1.24	1.20
Upper respiratory infection	1.08	0.57	0.54	0.50	0.54
Infection requiring hospitalization or IV antibiotics	0.03	0.08	0.02	0	0.03

[a] 6 months of etanercept as monotherapy in subjects with late-stage RA

[b] 6 months of etanercept added to background MTX in subjects with late-stage RA

[c] 1 year of etanercept as monotherapy in early RA

[d] 6 months of etanercept as monotherapy

7. Risk-Benefit Assessment

Currently, no disease-modifying therapies or biologic therapies are approved in the US for patients with AS. Many patients have unacceptable pain, stiffness, progressive immobility, and disability despite treatment with NSAIDS and other therapies.

The data from the 3 studies described in this briefing document demonstrate that etanercept acts rapidly and remarkably effectively in reducing signs and symptoms, increasing mobility, and improving laboratory markers of inflammation in patients with AS.

The etanercept safety profile in AS is favorable and comparable to the well-established safety profile observed in the treatment of other rheumatic diseases. This pattern of compelling efficacy with excellent tolerability constitutes a highly favorable risk-benefit profile, and establishes etanercept as a significant advance in therapy for patients afflicted by AS.

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Appendix 1: Efficacy and Safety Definitions and Instruments for Assessment of AS in Clinical Trials

1. Efficacy Definitions

Studies 016.0037 and 47687 used the following definitions for composite response criteria.

ASAS 20

An improvement of at least 20% and absolute improvement of at least 10 units on a 0 to 100-mm VAS scale in at least 3 of the following 4 domains:

Inflammation:	represented by the average of the last 2 questions on the 6-question BASDAI (Garrett et al, 1994) 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.”
Pain:	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”.
Function:	represented by the BASFI (Calin et al, 1994): average of 10 questions regarding ability to perform specific tasks as measured by VAS with extremes labeled “easy” and “impossible.”
Patient global assessment:	measured on a VAS scale with extremes labeled “none” and “severe.”

For a patient to be considered a responder, there could not be deterioration in the potential fourth domain. Deterioration was defined as a worsening of at least 20% and absolute change of at least 10 units (on a 0 to 100-mm VAS scale).

ASAS 50

For Study 016.0037, the ASAS 50 required an improvement of at least 50% and absolute improvement of at least 10 units on a 0 to 100-mm scale in at least 3 of the 4 domains with an absence of deterioration in the remaining domain. Absence of deterioration was defined as for the ASAS 20. For Study 47687 the ASAS 50 did not

require an absolute change of 10 or more units. Absence of deterioration was defined as for the ASAS 20.

ASAS 70

The ASAS 70 was defined for each study in a similar manner as the ASAS 50 except requiring improvement of at least 70% in at least 3 of the 4 domains.

Partial Remission of AS

Partial remission is defined as a value of < 20 units (scale 0 to 100) in each of 4 domains of the ASAS 20.

DCART 20

The DCART 20 response was defined as a composite score that combines the 4 criteria of the ASAS 20 with 2 additional criteria: improvement in a measure of spinal mobility and improvement in acute phase reactants. The prespecified measures of spinal mobility and acute phase reactant were chest expansion and CRP, respectively. The DCART 20 response requires a 20% improvement in 5 of the 6 criteria, with no worsening in the remaining criterion. Improvement and worsening for the 4 criteria of the ASAS 20 are defined above. Improvement and worsening for the measures of spinal mobility and acute phase reactant were based strictly on a 20% improvement or worsening relative to baseline, with no requirement of absolute change.

DCART 40

The DCART 40 requires a 40% improvement relative to baseline plus absolute improvement of at least 20 units in 3 of the 4 ASAS 20 criteria, with no worsening in the remaining criterion. Worsening was defined as for the ASAS 20.

2. Safety Definitions

Adverse Events

The types and intensities (grades) of adverse events (infectious and non-infectious) were tabulated. Injection site reactions and infections were collected on separate forms than the non-infectious adverse events. Events were graded (1 = mild, 2 = moderate, 3 = severe, or 4 = life-threatening) using a modified NCI Common Toxicity Criteria Scale. Events were classified using a modified Coding Symbols for a Thesaurus of Adverse

Reaction Terms dictionary (COSTART 1990) and summarized at the term level. Studies 016.0037 and 47687 used the same COSTART dictionary. For each patient, the most severe intensity of all occurrences of an event was tabulated in the summaries.

Serious Adverse Events

21 CFR 312.32 defines an adverse event as serious (SAE) if it results in death, is life-threatening, results in permanent or significant disability, results in drug dependency or abuse, requires patient hospitalization or prolongs hospitalization, is a congenital anomaly, or is a symptomatic overdose. An SAE also includes any important medical event that jeopardizes the patient or requires medical or surgical intervention to prevent one of the outcomes listed.

Laboratory Results

Laboratory results were categorized using a modified NCI Common Toxicity Criteria Scale and the laboratory's normal ranges. Toxicities noted before and during the study were summarized.

Anti-etanercept antibodies

Serum samples were analyzed by ELISA for the detection of antibody to etanercept. Test samples that were positive in the ELISA were tested for the presence of neutralizing antibodies to etanercept. Neutralizing antibodies are those that interfere with the binding of TNF to the receptor portion of etanercept.

3. Instruments for Assessment of AS in Clinical Trials

Physical Function - Bath AS Functional Index (BASFI)

The BASFI is a series of 8 questions regarding function in AS and 2 questions regarding the patient's ability to cope with everyday life (see Appendix Table 1 below). Each question is measured on a 100-mm VAS, the mean of which gives the BASFI. Subjects are asked about their ability to perform activities of daily living, including reaching up to shelves, putting on socks, standing unsupported, etc., and given a choice to answer between the extremes of "easy" or "impossible". The index was developed to address shortcomings in other functional indices, including the Dougados Functional Index and Stanford Health Assessment Questionnaire (Calin et al, 1994).

Appendix Table 1. The Bath Ankylosing Spondylitis Functional Index

PLEASE DRAW A MARK ON EACH LINE BELOW TO INDICATE YOUR ABILITY WITH EACH OF THE FOLLOWING ACTIVITIES DURING THE PAST WEEK: (AN AID IS A PIECE OF EQUIPMENT WHICH HELPS YOU TO PERFORM AN ACTION OF MOVEMENT)

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

EASY----------IMPOSSIBLE

Bending forward from the waist to pick up a pen from the floor without an aid

EASY----------IMPOSSIBLE

Reaching up to a high shelf without help or aids (eg, helping hand)

EASY----------IMPOSSIBLE

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

EASY----------IMPOSSIBLE

Getting up off the floor without help from lying on your back

EASY----------IMPOSSIBLE

Standing unsupported for 10 minutes without discomfort

EASY----------IMPOSSIBLE

Climbing 12-15 steps without using a handrail or walking aid. **One foot on each step**

EASY----------IMPOSSIBLE

Looking over your shoulder without turning your body

EASY----------IMPOSSIBLE

Doing physically demanding activities (eg, physiotherapy exercises, gardening or sports)

EASY----------IMPOSSIBLE

Doing a full days activities whether it be at home or at work

EASY----------IMPOSSIBLE

Physical Function - Dougados Functional Index (DFI)

The DFI is a 20-item patient questionnaire is used to assess patient function.

Pain - Nocturnal Pain

Amount of pain each patient experienced at night, as measured on a 100-mm VAS (with extremes of the scale from “no pain” to “most severe pain”)

Pain - Total Back Pain

Amount of total back pain patient experienced, as measured on a 100-mm VAS (with extremes of the scale from “no pain” to “most severe pain”)

Spinal Mobility - Modified Schober’s Test

The Modified Schober’s Test is measured by marking, with the patient standing fully erect, the midpoint of a line between the superior iliac spines and a point 10 cm above this point. The distance in cm between the 2 points is then measured after the patient is asked to bend maximally forward with knees locked.

Spinal Mobility - Chest Expansion Score

The chest expansion score is a measure of the difference in chest circumference in cm at the nipple line between maximal inspiration and maximal expiration.

Spinal Mobility – Occiput-To-Wall Measurement

The occiput-to-wall measurement is the distance in cm between the wall and the occiput with the patient standing with his/her back against the wall.

Patient Global Assessment

In each study the patient global assessment was measured using a VAS with a range of 0 to 100, or by using a 5-point scale (with “none” and “very severe”). In Study 0016.0037 and Study 47687, the 100-mm VAS was used.

Inflammation - BASDAI morning stiffness duration/intensity

The last 2 of the 6 questions of the BASDAI have been incorporated into the overall ASAS Working Group Definition of Short-Term Improvement as a measure of inflammation. These questions are related to the duration and intensity of morning stiffness and are measured on a 100-mm VAS. The first asks “How would you describe the overall level of morning stiffness you had from the time you wake up?” and allows a range of choices on a VAS from “none” to “very severe”. The second asks on a VAS (on

a scale from 0 to 2 hours) “How long does your morning stiffness last from the time you wake up?”

Inflammation - CRP

C-reactive protein is an acute phase reactant plasma protein that rises rapidly in response to infection or tissue injury.

Inflammation - Westergren sedimentation rate (ESR)

The erythrocyte sedimentation rate is an acute phase reactant that rises in response to infection or tissue injury.

The Bath Ankylosing Spondylitis Disease Activity Index

The (BASDAI) is a self-administered series of questions regarding fatigue, spinal and peripheral joint pain, and localized tenderness and morning stiffness (both qualitative and quantitative) measured on 6 horizontal, 100-mm VAS (see Appendix Table 2 below). It has been found to be useful, reliable, sensitive-to-change, and comprehensive measure of disease activity for subjects with ankylosing spondylitis (Garrett et al, 1994).

Appendix Table 2. The BASDAI

PLEASE PLACE A MARK ON EACH LINE BELOW TO INDICATE YOUR ANSWER TO EACH QUESTION, RELATING TO THE PAST WEEK

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

NONE----------VERY SEVERE

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

NONE----------VERY SEVERE

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

NONE----------VERY SEVERE

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

NONE----------VERY SEVERE

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

NONE----------VERY SEVERE

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

0 hours---------I---------I---------I---------I---------I---------I---------I---------I 2 or more hours

½ hour 1 hour 1 and ½ hour

Physician/Assessor Assessment

This instrument measures on a 100-mm VAS with extremes labeled “none” and “severe”.

Peripheral Tender and Swollen Joint Count

Symptoms of peripheral joint synovitis/enthesitis are hallmarks of active inflammation in patients with AS and were considered by the ASAS Working Group to be important parameters for assessment of short-term outcomes in patients with this disease, although these measures individually were not ultimately included in the ASAS core composite response criteria for measurement of short-term symptomatic improvement (they were, however, included in measures of “disease-controlling” therapies) (Van der Heijde et al, 1998).

Modified Enthesopathy Index

Performed by applying uniform manual pressure to vertebral processes C1-C2, C7-T1, T12-L1, L5-S1, the symphysis pubis, both greater trochanters, pelvis abductor origin, anterior superior border of the iliac crests, ischial tuberosities, insertions of Achilles tendons, and plantar fascia; tenderness scored on a 4-point scale (0=no pain, 1= mild tenderness, 2=moderate tenderness, 3= wince or withdrawal); total score subjected to analysis.

Krupp's Fatigue Severity Scale

This instrument is comprised of 9 statements relating to fatigue that subjects 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 Short-Form Health Survey (SF-36)

A 36-item questionnaire comprising 8 scales: physical functioning, role limitations attributable to physical or emotional problems, social functioning, general health, vitality, bodily pain, and mental health. The SF-36 can be converted into 2 summary scores: a physical component summary (PCS) and a mental component summary (MCS), which are linear combinations of the 8 scales.