Outcomes of a Multicentre Randomised Clinical Trial of Etanercept to Treat Ankylosing Spondylitis

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Outcomes of a Multicentre Randomised Clinical Trial of Etanercept to Treat Ankylosing Spondylitis

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Abstract

Objective: A double-blind, randomised, placebo-controlled study evaluated the safety and efficacy of etanercept to treat adult patients with ankylosing spondylitis (AS).

Methods: Adult patients with AS at 14 European sites were randomly assigned to 25-mg injections of etanercept or placebo twice weekly for 12 weeks. The primary efficacy endpoint was an improvement of at least 20% in patient-reported symptoms, based on the multicomponent Assessments in Ankylosing Spondylitis (ASAS) response criteria (ASAS 20). Secondary endpoints included ASAS 50 and ASAS 70 responses and improved scores on individual components of ASAS, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), acute phase reactants, and spinal mobility tests. Safety was evaluated during scheduled visits.

Results: Of 84 patients enrolled, 45 received etanercept and 39 received placebo. Significantly more etanercept patients than placebo patients responded at the ASAS 20 level as early as week 2, and sustained differences were evident through week 12. Significantly more etanercept patients reported ASAS 50 responses at all time points and ASAS 70 responses at weeks 2, 4, and 8; reported lower composite and fatigue BASDAI scores; had lower acute phase reactant levels; and had improved spinal flexion. Etanercept was well tolerated. Most adverse events were mild to moderate; the only between-group difference was injection site reactions, which occurred significantly more often in etanercept patients.

Conclusions: Etanercept is well-tolerated and effective therapy for reducing clinical symptoms and signs of AS.
Key Words (maximum is 5)

Ankylosing spondylitis
Assessments in Ankylosing Spondylitis (ASAS)
Etanercept
Tumour necrosis factor [inhibitors]
Biological therapy
Introduction

Ankylosing spondylitis (AS) is an underrecognized, debilitating disease predominantly affecting the spine that is characterised by axial skeletal ankylosis and inflammation at the insertions of tendons. Its (AS) prevalence is most clearly described in the Caucasian population where a link to HLA B-27 antigen is best defined, and is believed to be around 0.5%, with estimations ranging from 0.1% to 1.1%. Peripheral joints also may be involved. The disease occurs 3 times more often in men than in women, and onset typically occurs between 20 and 40 years of age. Although AS advances slowly, damage to the spine is progressive and leads to pain, fatigue, stiffness, and functional impairment. Patients with AS often have a restricted or poor quality of life and may face a reduced life expectancy. The socio-economic burden of their disease can be considerable, owing to work disabilities and the use of health care/assistance resources, and sometimes to the patient’s depressed mood or low social functioning. Current therapeutic options for AS, such as nonsteroidal anti-inflammatory drugs (NSAIDs), offer temporary pain relief but confer little if any clinical benefit on spinal mobility. Disease-modifying antirheumatic drugs (DMARDs), including methotrexate and sulphasalazine, may benefit peripheral arthritis but do not appear to affect the spinal involvement of AS.

Tumour necrosis factor (TNF) alpha, TNFα, is a pro-inflammatory cytokine that appears to play a key role in the pathogenesis of AS disease. Etanercept is a fully human recombinant protein, consisting of 2 molecules of soluble TNF receptor p75 and the crystalisable fragment component of immunoglobulin G1, which specifically binds to and neutralises TNFα. Etanercept is effective in the treatment of other TNF-related diseases, including rheumatoid arthritis (RA), juvenile chronic arthritis, and psoriatic arthritis (PsA). More recently, a phase 2 clinical study has shown that etanercept reduces disease activity...
in patients with spondyloarthopathies, including reactive arthritis and AS. Similar results have been reported with infliximab, a chimeric monoclonal antibody against TNFα.

The current double-blind, randomised, multicentre European trial examined the efficacy of etanercept to treat AS in adults, using the recently published criteria of an international consortium of experts, the Assessments in Ankylosing Spondylitis (ASAS) Working Group. Previous etanercept trials in AS have been conducted at both North American and European investigative sites. This study is the first conducted exclusively at European centers. Since there are potentially important differences between populations studied and in the way patients are treated in different geographic locations, it was important to this study to confirm the results of a multinational study of etanercept that was conducted concurrently. These trials are the first studies performed with anti-TNF biologic agents using the ASAS response criteria as the primary endpoints.
Methods

Study Design. A double-blind, randomised, placebo-controlled study was conducted to evaluate the efficacy and safety of etanercept in the treatment of adult patients with active AS. The study took place from March 2002 to August 2002 in 14 investigative centres in 8 countries: Belgium, Finland, France, Germany, Italy, The Netherlands, Spain, and the United Kingdom. All centres received approvals from their independent ethics committees, and all patients provided written informed consent to participate. The study included a screening period of up to 4 weeks, followed by a 12-week treatment period in which patients received etanercept or placebo. Efficacy and safety evaluations were performed at weeks 2, 4, 8, and 12.

Patients. Patients aged 18 to 70 years with active AS were eligible for the study. AS was diagnosed using the modified New York criteria. Disease activity was measured using a set of visual analog scales (VAS) on which patients rated the severity of their symptoms from 0 (none) to 100 (most severe) in 4 symptom domains: (1) spinal inflammation, (2) back pain, (3) patient global assessment of disease activity, and (4) physical function. Active disease was diagnosed if the patient had an average score ≥ 30 for spinal inflammation and a score ≥ 30 on at least 2 of the other 3 domains.

Patients were excluded if they had complete ankylosis (fusion) of the spine; previously used TNFα inhibitors, including etanercept; used DMARDs other than hydroxychloroquine, sulphasalazine, or methotrexate within 4 weeks of baseline; used multiple NSAIDs; used > 10 mg prednisone daily; or changed doses of NSAIDs or prednisone within 2 weeks of baseline. Patients were permitted to continue prestudy physiotherapy.

Patients who met eligibility criteria were stratified on the basis of concomitant DMARD use at baseline and randomly assigned to receive etanercept or placebo. The protocol did not require screening for tuberculosis.
**Study Product.** Based on previous clinical trials of etanercept in patients with RA and PsA, a 25-mg dose delivered subcutaneously twice weekly was selected for patients with AS. Patients self-administered the product and were given individual packages containing injection supplies and instructions for storage and use. To preserve the integrity of the blind, placebo supplies were similar in appearance to etanercept supplies.

**Efficacy Endpoints.** The clinical response to etanercept was evaluated chiefly on the basis of response criteria recommended by the ASAS Working Group, which covered the same 4 domains used in this study to assess disease activity at enrollment, ie, spinal inflammation, back pain, patient global assessment, and physical impairment. Spinal inflammation was scored as the average of 2 VAS questions about the duration and intensity of morning stiffness, taken from the previously validated 6-item Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Pain was scored as the average of 2 VAS questions about total back pain and nocturnal back pain. Patient global assessment was measured by VAS. Functional impairment was assessed by the 10-item Bath Ankylosing Spondylitis Functional Index (BASFI), a validated VAS-based composite of functional ability in patients with AS. Details on the BASDAI and BASFI indexes and other efficacy endpoints appear in Table 1.

The primary efficacy endpoint was the percentage of ASAS 20 responders after 12 weeks of treatment. ASAS 20 responders were patients who reported improvements of at least 20% and absolute improvement of at least 10 units in at least 3 of the 4 symptom domains, with no worsening in the remaining domain. Secondary endpoints included the percentage of ASAS 20 responders at weeks 2, 4, and 8; the percentage of patients improving 50% or more (ASAS 50) at any visit; and the percentage improving 70% or more (ASAS 70) at any visit. ASAS 50 and 70 responses also required improvement in at least 3 domains and a lack of deterioration in the remaining domain. Other patient-reported endpoints consisted of
symptom improvements in individual ASAS domains and improvements on the composite BASDAI and its individual components. Effects on acute phase reactants were measured by tests for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Effects on spinal mobility were measured by Schober’s test, chest expansion, and occiput-to-wall distance.

**Safety Analyses.** Patients were monitored for adverse events and abnormal laboratory test results over the course of the study. Vital signs were monitored, and standard hematology, serum chemistry, and urinalysis tests were evaluated. In addition, blood samples were tested for antibody to etanercept at baseline and at week 12, using an ELISA assay modified from the method published earlier.

**Statistics.** Disease activity and safety analyses were based on the intent-to-treat population and included all patients who received at least 1 dose of blinded test article. The last-observation-carried-forward technique was used to handle missing data for continuous and ordinal endpoints. Patients who withdrew from the study prematurely were treated as nonresponders at each assessment interval thereafter for ASAS and other patient-reported responses. All statistical tests were 2-sided. The Cochran-Mantel-Haenszel test, stratified by baseline DMARD use, was used to evaluate efficacy differences between the etanercept and placebo groups, and chi square and Breslow-Day tests were used to evaluate direct and interactive effects of DMARDs on ASAS responses. For safety analyses, the Fisher exact test was used to compare the percentage of adverse events occurring in etanercept- and placebo-treated groups. Based on a previous trial, week 12 response rates of 35% in the placebo group and 75% in the Etanercept group were expected. Assuming similar response rates, this study design provided 90% power with 40 patients per group.
Results

**Study Objective.** This study was conducted to evaluate the safety and efficacy of etanercept to treat adult patients with ankylosing spondylitis.

**Patient Recruitment and Retention.** A total of 84 patients were enrolled in the study; 45 were assigned to receive etanercept and 39 were assigned to placebo. The average age of patients was 43.2 years. Most participants were male (79%), and the majority were white (94%). The treatment groups were similar in baseline disease activity scores and concomitant use of DMARDs, NSAIDs, and corticosteroids. Demographic characteristics were largely similar, except that etanercept patients were, on average, 5 years older than placebo patients and had had AS disease for 5 years longer (Table 2) and also had a significantly higher baseline CRP levels (Table 4).

Two (2) etanercept-treated patients discontinued from the study for non-safety reasons. The first patient discontinued after a single dose of etanercept because he did not meet the inclusion criterion of active disease, and the second patient withdrew his consent 8 days after therapy was initiated. Both patients were treated as nonresponders at subsequent time points. The remaining 82 patients completed the study.

**Efficacy Results.** Significantly more etanercept patients than placebo patients (60% versus 23.1%; \( p < 0.001; 95\% \text{ CI: 17.4-56.4\%} \)) were ASAS 20 responders at week 12, the primary efficacy endpoint. The primary endpoint was not significantly affected by the concomitant use of DMARDs (\( p = 0.632 \)), nor was there an interaction effect between DMARDs and etanercept on ASAS 20 at week 12 (\( p = 0.694 \)).

Significant improvements in the etanercept group were evident by week 2, the earliest assessment point, and were sustained thereafter (Figure 1a). There were also significantly more responders in the etanercept group at the ASAS 50 level at all visits (\( p < 0.01 \)) and at the ASAS 70 level at weeks 2, 4, and 8 (\( p < 0.05 \)) (Figures 1b and 1c). By week 12, nearly
half of the patients treated with etanercept improved 50% or more on the ASAS criteria, and a quarter of them improved 70% or more.

ASAS responses used in this study were based on the average of total and nocturnal back pain. The ASAS Working Group criteria, published after plans for this study were completed, recommended using VAS for total back pain only. Sensitivity analyses using total pain scores alone confirmed nearly identical results to those reported here.

In addition to improved responses on the overall ASAS criteria, etanercept patients significantly improved their mean scores on the individual ASAS components (p < 0.01 versus placebo). Scores of etanercept patients improved 43% on both the spinal inflammation and back pain measures, 37% on patient global assessment of disease activity, and 35% on the functional impairment index (compared with 16%, 6%, 13%, and 3% improvements, respectively, for placebo patients; Table 3). Although scores on individual components of BASFI are not provided in this paper, etanercept was significantly more effective than placebo in improving 9 of 10 types of functional abilities.

Scores on the BASDAI composite index and the BASDAI fatigue component improved 43% among etanercept patients (p < 0.01 versus placebo). In addition, a post hoc analysis of BASDAI responses revealed that the percentage of etanercept patients with BASDAI scores less than 40 increased from 9% at baseline to 71% at week 12 (Figure 2).
Acute phase reactants, CRP and ESR, also significantly decreased in etanercept patients ($p < 0.0001$), with percentage changes of 70% and 80%, respectively (Table 4). Spinal flexion, as measured by Schober’s test, improved in etanercept-treated patients but not in placebo patients ($p < 0.01$). Other measures of spinal mobility also improved more in etanercept patients, but the differences were not statistically significant.

Patients in this trial had limited peripheral joint disease. Swollen and tender joints were 2 and 6, respectively, for the entire population. Given the paucity of this data, no meaningful results on peripheral joint disease were obtained.

**Safety Results.** Etanercept therapy was generally well tolerated. Adverse events were mostly mild to moderate, and there were no safety-related discontinuations. Treatment-emergent adverse events (TEAEs) reported by 5% or more of patients in either treatment group were generally similar (Table 5). As in previous studies of etanercept, injection site reactions occurred significantly more often in etanercept patients (33.3%) than in placebo patients (15.4%, $p < 0.05$). No antibodies to etanercept were detected.

One serious adverse event was reported. An etanercept-treated patient with acute myocardial infarction underwent angioplasty but continued in the study. The same patient developed grade 3 abnormality of liver function test results at the week 12 visit, which was considered to be related to concomitant indomethacin therapy. The abnormalities resolved after indomethacin was discontinued, and the patient completed the study.
Discussion

AS is a chronic inflammatory disease, often leading to permanent spinal damage, a considerable handicap, and a poor quality of life. Current treatments for AS are inadequate for most patients, especially treatments for axial skeletal involvement.

In this 12-week study, twice-weekly self-administered injections of 25 mg of etanercept produced rapid, significant, and sustained improvement in multiple clinical and biological measures of AS, regardless of concomitant DMARD use. Patient improvements were evident at the 2-week visit and were sustained through the end of the study at week 12. Notably, the only differences between groups at baseline were that etanercept patients were on average 5 years older, had had AS for 5 years longer than patients receiving placebo and had higher baseline CRP levels. Given the magnitude of the etanercept treatment response in this study, it is unlikely that these baseline differences affected results in any significant way. Furthermore, in light of recent analyses indicating that older patients and patients with longer disease duration are less likely to have a major clinical response to TNFα inhibitors, this group’s demonstrable response to etanercept is particularly encouraging.

The finding of multiple positive effects in this study of European patients supports the results of two other efficacy and safety studies of etanercept to treat AS. The first was a 16-week US study, which showed that etanercept was efficacious in the treatment of many AS patient-reported symptoms, including pain, vitality, and physical function. The second was a 24-week multinational study that was conducted concurrently with the present study and included similar endpoints. Using the ASAS benchmarks of 20%, 50%, and 70% improvement, both the current study and the 24-week study found etanercept treatment to be significantly superior to placebo, with robust improvements occurring as early as week 2.

Treatment with etanercept also improved BASDAI scores; by week 12, 71% of etanercept-treated patients achieved BASDAI scores less than 40, which the ASAS Working
Group considers as the threshold value indicating a need for anti-TNFα therapy. Moreover, fatigue scores, which are felt to be an important outcome in AS, improved significantly with etanercept therapy. Because fatigue is associated not only with disease activity and functional ability but also with patients’ global sense of well-being and mental health status, improvement in this area may lead to a better quality of life for AS patients.

In the current study, CRP levels and ESR values significantly decreased in patients taking etanercept, which may be indicative of disease modification, not just symptomatic relief of AS. Spinal mobility, as measured by Schober’s test, significantly improved in etanercept-treated patients, which suggests that damage caused by AS may not be permanent. The lack of significant between-group differences in chest expansion and occiput-to-wall distances at the end of treatment may be due to the short duration of the study and/or relatively small number of patients enrolled. In the 24-week study mentioned earlier, which enrolled more patients, all three spinal mobility measures significantly improved with etanercept therapy. Due to the short duration of this trial, the impressive therapeutic results must interpreted with some caution. Nonetheless, the relative ineffectiveness of current treatments such as DMARDs and NSAIDs is underscored by the fact that etanercept–treated patients who remained on these treatments enjoyed no apparent efficacious advantage over those who were not receiving these medications.

The efficacy results are also consistent with those reported for infliximab; however, no antibodies to etanercept were found in this study. Although the lack of etanercept immunogenicity in this trial could be explained by the trial’s brevity and the frequency of etanercept antibodies after long-term treatment in patients with AS is unknown. It is noteworthy, however, that in etanercept trials of up to 2 years in patients with RA, the level of etanercept antibodies reactivity has been reported in the range of 3%. Additionally, these results contrast with the recent finding of a study of infliximab to treat
Crohn’s disease, in which 61% of patients produced antibodies to infliximab after a mean of 3.9 infusions 5 mg/kg infusions over a mean of 10 months. In the latter study, antibody concentrations \( \geq 8.0 \text{ µg/mL} \) significantly reduced serum concentrations of infliximab, which in turn significantly decreased the duration of treatment response.52

Etanercept was well tolerated in adult patients with AS. Although approximately one-third of patients had injection site reactions, no serious infections occurred, and no patients withdrew because of these reactions or other adverse events. Etanercept’s safety profile was similar to that seen in patients with RA and PsA. Although pharmacokinetic (PK) parameters from the current study are not shown in this article, a separate analysis of clearance and steady-state trough concentrations showed that etanercept’s PK profile in patients with AS was similar to that in patients with RA;63 thus, it appears that the disposition of etanercept is unaltered by the AS disease state.

As noted out above the socio-economic burden of AS can be considerable. Thus, the relatively higher cost of etanercept therapy compared to less efficacious treatments should be weighed against the costs of AS disease.

In summary, etanercept produced a rapid and sustained reduction of the clinical signs and symptoms of AS. Given these results, further investigation of longer-term treatment with etanercept is warranted to further define its therapeutic utility. The use of imaging tools also is warranted to investigate the effects of etanercept on spinal disease, and such tests may shed light on whether etanercept is able to halt the progression of AS.
Acknowledgments

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References


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Table 1. Efficacy Endpoints Used to Assess Etanercept

I. ASAS Response Criteria: improvements of at least 20%, 50%, and 70% in at least 3 of these 4 domains:
   A. Spinal inflammation: composite of 2 items from BASDAI, ie,
      1. Duration of morning stiffness
      2. Intensity of morning stiffness
   B. Total back pain and nocturnal back pain (combined)
   C. Patient global assessment of health
   D. Functional impairment: composite score of 10 items on BASFI, ie,
      1. Putting on socks without aids
      2. Picking up pen from floor
      3. Reaching high shelf without aids
      4. Getting up from an armless chair
      5. Getting off floor from back
      6. Standing unsupported for at least 10 minutes
      7. Climbing 12 to 15 steps without aids
      8. Looking over shoulder
      9. Performing a demanding activity
     10. Doing a full day’s activity

II. BASDAI Scores
   A. Daily activity composite score
   B. Scores on 6 separate items
      1. Fatigue
      2. AS pain in necks, back, or hips
      3. Pain in other joints
      4. Discomfort in areas tender to touch or pressure
      5. Duration of morning stiffness
      6. Intensity of morning stiffness
III. Levels of Acute Phase Reactants
   A. C-reactive protein (CRP)
   B. Erythrocyte sedimentation rate (ESR)

IV. Spinal Mobility Scores
   A. Forward flexion (Schober’s test)
   B. Chest expansion
   C. Occiput-to-wall distance

ASAS = Assessments in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index;
BASFI = Bath Ankylosing Spondylitis Functional Index
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 84)</th>
<th>Placebo (n = 39)</th>
<th>Etanercept (n = 45)</th>
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</thead>
<tbody>
<tr>
<td>Mean age, years ± SD</td>
<td>43.2 ± 10.6</td>
<td>40.7 ± 11.4</td>
<td>45.3 ± 9.5*</td>
</tr>
<tr>
<td>Sex, % men/women</td>
<td>79/21</td>
<td>77/23</td>
<td>80/20</td>
</tr>
<tr>
<td>Race, % white/other</td>
<td>94/6</td>
<td>95/5</td>
<td>93/7</td>
</tr>
<tr>
<td>Mean disease duration, years ± SD</td>
<td>12.5 ± 8.9</td>
<td>9.7 ± 8.2</td>
<td>15.0 ± 8.8**</td>
</tr>
<tr>
<td>Concomitant use of DMARD,1 n (%)</td>
<td>32 (38)</td>
<td>16 (41)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>1 (1)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>11 (13)</td>
<td>5 (13)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>22 (26)</td>
<td>11 (28)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Concomitant use of oral NSAID, n (%)</td>
<td>73 (87)</td>
<td>33 (85)</td>
<td>40 (89)</td>
</tr>
<tr>
<td>Concomitant use of corticosteroid, n (%)</td>
<td>13 (15)</td>
<td>6 (15)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Mean scores on ASAS components:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal inflammation</td>
<td>65.4</td>
<td>62.9</td>
<td>67.5</td>
</tr>
<tr>
<td>Nocturnal and total back pain</td>
<td>58.2</td>
<td>56.1</td>
<td>60.0</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>64.6</td>
<td>63.4</td>
<td>65.6</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>58.8</td>
<td>57.2</td>
<td>60.2</td>
</tr>
<tr>
<td>Mean BASDAI scores overall</td>
<td>59.9</td>
<td>58.6</td>
<td>61.0</td>
</tr>
<tr>
<td>BASDAI scores &lt; 40, n (%)</td>
<td>10 (12)</td>
<td>5 (15)</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>
One (1) patient in each group took more than one DMARD. DMARD = disease-modifying antirheumatic drug.

* p < 0.05 versus placebo, by ANOVA.

** p < 0.01 versus placebo, by ANOVA.
Table 3. Comparison of ASAS and BASDAI Scores
Before and After 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Response Parameter</th>
<th>Placebo (n = 39)</th>
<th>Etanercept (n = 45)</th>
<th>p-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASAS: Spinal inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>62.9</td>
<td>67.5</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>52.6 (15.9)</td>
<td>35.6 (43.3)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>ASAS: Nocturnal and total pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>56.1</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>51.2 (6.2)</td>
<td>31.0 (43.1)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>ASAS: Patient global assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>63.4</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>54.1 (12.6)</td>
<td>38.4 (37.0)</td>
<td>0.011</td>
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<tr>
<td><strong>ASAS: Functional impairment (BASFI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>57.2</td>
<td>60.2</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>53.9 (3.4)</td>
<td>39.6 (35.4)</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>BASDAI: Composite score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>58.6</td>
<td>61.0</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>50.1 (13.6)</td>
<td>33.8 (43.6)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>BASDAI: Fatigue score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>59.0</td>
<td>68.2</td>
<td></td>
</tr>
<tr>
<td>Week 12 (% change)</td>
<td>54.8 (-4.9)</td>
<td>38.4 (42.6)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Differences in mean percent change, baseline to week 12, by the Cochran-Mantel-Haenszel test. ASAS = Assessments in Ankylosing Spondylitis; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.
Table 4. Comparison of Acute Phase Reactants and Spinal Mobility Values
Before and After 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Assessment Point</th>
<th>Placebo</th>
<th>Etanercept</th>
<th>p-Value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>Baseline median</td>
<td>n = 39</td>
<td>n = 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.7</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 12 (% change)</td>
<td>11.7 (0.0)</td>
<td>4.0 (69.5)</td>
<td>0.000</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>Baseline median</td>
<td>n = 39</td>
<td>n = 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.0</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 12 (% change)</td>
<td>29.0 (0.0)</td>
<td>6.0 (79.6)</td>
<td>0.000</td>
</tr>
<tr>
<td>Schober’s test of spinal flexion, cm</td>
<td>Baseline mean</td>
<td>n = 39</td>
<td>n = 44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 12 (% change)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2.7 (1.3)</td>
<td>2.7 (-36.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Chest expansion, cm</td>
<td>Baseline mean</td>
<td>n = 39</td>
<td>n = 44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.9</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 12 (% change)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.1 (-9.0)</td>
<td>3.8 (-29.9)</td>
<td>0.870</td>
</tr>
<tr>
<td>Occiput-to-wall distance, cm</td>
<td>Baseline mean</td>
<td>n = 22&lt;sup&gt;3&lt;/sup&gt;</td>
<td>n = 32&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.6</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week 12 (% change)</td>
<td>4.0 (7.2)</td>
<td>6.2 (12.5)</td>
<td>0.065</td>
</tr>
</tbody>
</table>
Differences in average percent change, baseline to week 12, by the Cochran-Mantel-Haenszel test.

Negative percent change from baseline indicates improvement.

Includes only patients who had a value greater than zero at baseline.
Table 5. Number (%) of Patients with Treatment-Emergent Adverse Events or Infections (Occurring in ≥ 5% of Patients in Either Treatment Group)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 39)</th>
<th>Etanercept (n = 45)</th>
<th>p-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>6 (15.4)</td>
<td>15 (33.3)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hemorrhage, injection site</td>
<td>4 (10.3)</td>
<td>8 (17.8)</td>
<td>0.367</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (10.3)</td>
<td>6 (13.3)</td>
<td>0.745</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (10.3)</td>
<td>3 (6.7)</td>
<td>0.699</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (2.6)</td>
<td>5 (11.1)</td>
<td>0.209</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (7.7)</td>
<td>0</td>
<td>0.096</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (5.1)</td>
<td>2 (4.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (5.1)</td>
<td>2 (4.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pain, abdomen</td>
<td>2 (5.1)</td>
<td>1 (2.2)</td>
<td>0.595</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>2 (5.1)</td>
<td>1 (2.2)</td>
<td>0.595</td>
</tr>
<tr>
<td>Arthalgia</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0.213</td>
</tr>
<tr>
<td>Hemorrhage, gastrointestinal</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0.213</td>
</tr>
<tr>
<td>Injury accidental</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0.213</td>
</tr>
<tr>
<td>Pain, back</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0.213</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>2 (5.1)</td>
<td>0</td>
<td>0.213</td>
</tr>
</tbody>
</table>

¹ Difference in occurrence, by Fisher’s exact test.
Figure 1a

Figure 1b
Figure 1c

Figure 2