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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Enbrel® / Etanercept

PROTOCOL NO.: 0881A3-402-WW (B1801267)

PROTOCOL TITLE: A Randomized, Double-Blind Study Evaluating the Safety and Efficacy of Etanercept and Sulphasalazine in Subjects With Ankylosing Spondylitis

Study Centers: A total of 102 centers took part in study and enrolled subjects; 15 in Germany, 10 in France, 9 each in Italy and the United Kingdom (UK), 7 in Spain, 6 in Denmark, 5 in Hungary and the Netherlands, 4 each in Finland, Poland, and Serbia, 3 each in Austria and the Czech Republic, 2 each in Australia, China, Colombia, Greece, Ireland, Mexico, Portugal, and Sweden, and 1 each in Qatar and Switzerland.

Study Initiation and Final Completion Date: 19 December 2005 to 01 February 2008

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To compare the efficacy of etanercept 50 mg once weekly with sulphasalazine (SSZ) 3 g daily in the treatment of ankylosing spondylitis (AS) subjects over 16 weeks. The study hypothesis was that etanercept 50 mg once weekly would demonstrate superior clinical efficacy, as determined by the proportion of responders achieving a 20% improvement on the Assessment of AS (ASAS) response criteria (ASAS 20) at 16 weeks, compared with SSZ 3 g daily in the treatment of AS subjects.

Secondary Objectives:

- To compare the effect of etanercept 50 mg once weekly with SSZ 3 g daily on the quality of life over 16 weeks;
- To evaluate the safety of etanercept 50 mg once weekly over 16 weeks.

METHODS

Study Design: This was a randomized, double-blind, multicenter, active-comparator, parallel design, outpatient study. Screening of subjects was performed up to 4 weeks before randomization, and was followed by a treatment phase of 16 weeks.

Subjects were randomly assigned to receive either etanercept 50 mg once weekly or SSZ 3 g daily in a 2:1 allocation, respectively. Matching placebos for etanercept and SSZ were used to maintain the blinding. Subjects who received SSZ started the medication at 0.5 g daily for

the first week and increased the dose by 0.5 g every week until a daily dose of 3 g was achieved. Subjects who were unable to tolerate a daily dose of 3 g of SSZ could be treated with a lower dose, but the dose had to be at least 1.5 g daily. A follow-up telephone call was required approximately 15 days after the completion of study treatment to assess adverse events (AEs).

The total duration of participation in the study for a subject was approximately 22 weeks. This included the screening period of up to 4 weeks, 16-week treatment period, and the follow-up telephone call 15 days after completion of study treatment. The schedule of study assessments and procedures is presented in Table 1.

Table 1. Schedule of Study Activities

Study Week[a]	**Screening**[b] **-4 to 0**	**Baseline 0**	**2**	**4**	**8**	**12**	**16**	**18**	**Early Discontinuation**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**[c]	**99**
Informed consent	X								
Medical history	X								
Inclusion/exclusion criteria	X	X							
Prior medications	X	X							
Concomitant medications			X	X	X	X	X		X
Physical examination	X	X					X		X
Vital signs[d]	X	X	X	X	X	X	X		X
Joint assessment[e]	X	X[f]	X	X	X	X	X		X
Physician global assessments[e,g]	X	X[f]	X	X	X	X	X		X
BASMI[e]	X	X[f]	X	X	X	X	X		X
Occiput-to-wall distance[e]	X	X[f]	X	X	X	X	X		X
Chest expansion[e]	X	X[f]	X	X	X	X	X		X
Patient global assessments[g]	X	X[f]	X	X	X	X	X		X
Nocturnal and total back pain	X	X[f]	X	X	X	X	X		X
BASFI	X	X[f]	X	X	X	X	X		X
BASDAI	X	X[f]	X	X	X	X	X		X
EuroQoL-5 Dimensions (EQ-5D)		X					X		X
36-Item short-form health survey (SF-36)		X					X		X
Hospital Anxiety and Depression Scale (HADS)		X					X		X
Ankylosing Spondylitis Quality Of Life (ASQoL)[h]		X					X		X
Haywood Questionnaire		X					X		
Health Care Resource Utilization Questionnaire	X								
Pregnancy test[i]	X	X							
Urinalysis	X	X[f]					X		X
Chemistry and haematology	X	X[f]	X	X	X	X	X		X
C-reactive protein	X	X[f]	X	X	X	X	X		X
Human Leukocyte Antigen B27 (HLA-B27)[j]		X							
Pelvic X-ray[j]	X								
Chest X-ray[k]	X								
Adverse events		X	X	X	X	X	X	X	X
Randomisation		X							
Drug accountability			X	X	X	X	X		X
Dispense diary card		X	X	X	X	X			
Dispense test article[l] ie, study drug		X		X	X	X			

Table 1. Schedule of Study Activities

BASMI = Bath Ankylosing Spondylitis Metrology Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

a. A ±4-day window was permitted for Visit 2 through 7 (Week 0-16).
b. Screening and baseline visit could occur on the same day if subjects did not require a washout of prohibited medications. Women of childbearing potential, however, had to have both serum and urine pregnancy testing.
c. Follow-up telephone call to assess new and ongoing adverse events, occurring approximately 15 days after Visit 7 or early discontinuation.
d. Included sitting blood pressure and pulse rate; weight and height were recorded only at baseline.
e. It was recommended that the same qualified medical personnel complete these assessments at each of visit.
f. Waived if first dose within 14 days of screening evaluation.
g. Patient and physician global assessments of peripheral joint arthritis activity were done only if applicable.
h. Only administered on subjects for whom a valid translation of the instrument was available.
i. For women of childbearing potential only (serum test at screening visit, urine at baseline visit).
j. Waived if results were known and copy of report was in source documents.
k. Waived if within 3 months and report was available and was included in subject's source documents.
l. First dose administered after baseline evaluations were completed.

Number of Subjects (Planned and Analyzed): There were 540 subjects planned for the study at the allocation rate of 2:1 for etanercept and SSZ, respectively. A total of 566 subjects were randomized to receive study treatment (379 subjects to etanercept and 187 subjects to SSZ). All randomized subjects were analyzed for primary and secondary endpoints.

Diagnosis and Main Criteria for Inclusion: Males and females aged 18 years and older with clinical diagnosis of AS (as defined by Modified New York Criteria for AS) who had active AS were eligible to participate in the study. Subjects were to be excluded if they had complete ankylosis of the spine, had been treated with etanercept previously, or had received SSZ treatment within 6 months of screening.

Study Treatment: All subjects received subcutaneous injections of either etanercept 50 mg or matching placebo once weekly for 16 weeks. Additionally, all subjects had to take oral SSZ 0.5 g tablets or matching placebo once daily for the first week and twice daily, thereafter, per the titration schedule with a target dose of 3 g daily. To remain in the study, subjects had to take at least 1.5 g daily of SSZ.

Efficacy and Health Outcome Endpoints:

Efficacy Endpoints:

Primary Endpoint: The primary endpoint was the proportion of subjects who achieved ASAS 20 at Week 16 relative to baseline. This endpoint was derived from the 4 AS assessments (patient global assessment of disease activity, pain, physical function, and inflammation). If a subject had a missing evaluation for any 1 of the 4 AS assessment domains, the subject was considered to be a nonresponder at that time point when the subject was included in the analysis population.

Secondary Endpoints:

- Proportion of subjects who achieved ASAS 20 at time points other than Week 16;
- Proportion of subjects who achieved ASAS 40 at Week 16;
- Proportion of subjects who achieved ASAS 50 at Week 16;
- Proportion of subjects who achieved ASAS 70 at Week 16;
- Proportion of subjects who achieved ASAS 5/6 at Week 16;
- Change from baseline by visit in the Visual Analog Scale (VAS) patient global assessments;
- Change from baseline by visit in the VAS physician global assessments;
- Change from baseline by visit in the VAS assessment of nocturnal and total back pain;

- Change from baseline by visit in the Bath Ankylosing Spondylitis Functional Index (BASFI) and its components;
- Change from baseline by visit in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and its components;
- Proportion of subjects who achieved a 50% improvement in BASDAI by visit;
- Change from baseline by visit in the complete joint assessment (70 joints);
- Frequency and time to partial remission (partial remission was defined as a score of <20 on a 0 to 100 scale in each of the 4 ASAS 20 domains);
- Change from baseline by visit in the spinal mobility as measured by Bath Ankylosing Spondylitis Metrology Index (BASMI) and its 5 components (cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's and intermalleolar distance - each best of 2 tries), as well as occiput-to-wall distance and chest expansion (maximum - minimum, best of 2 tries);
- Proportion of subjects with evaluation <20 (on a scale of 0 to 100 mm) in each of the following 4 ASAS domains:
    - VAS patient global assessment;
    - VAS pain score represented by the average of VAS total and nocturnal pain scores;
    - BASFI;
    - BASDAI-2 morning stiffness-related scores;
- Change from baseline by visit in the acute phase reactant laboratory assessment of C-reactive protein (CRP).

Health Outcome Endpoints:

- Change from baseline to Week 16 in the European Quality of Life (EuroQoL)-5 Dimension (EQ-5D);
- Change from baseline to Week 16 in the 36-Item Short-Form Health Survey (SF-36) and its domains;
- Change from baseline to Week 16 in the Hospital Anxiety and Depression Scale (HADS);
- Change from baseline to Week 16 in the Ankylosing Spondylitis Quality of Life (ASQoL).

Safety Evaluations: Safety was assessed by evaluation of serious AEs (SAEs), AEs, vital sign measurements, physical examinations findings, premature withdrawals, and results of laboratory tests.

Statistical Methods:

Analysis Sets:

Modified Intent-to-Treat Population (mITT): All subjects who received at least 1 dose of study drug and had at least 1 post baseline efficacy evaluation. The mITT population was the primary population for efficacy analyses.

Efficacy Evaluable (Per-Protocol) Population: The efficacy evaluable population included all those members of the mITT population who had no protocol violations considered to possibly compromise interpretation of the efficacy results. Criteria and subjects to be excluded were determined before the study was unblinded. In case of small number of exclusions, there could be no analyses using the efficacy evaluable population.

Safety Population: All randomized subjects with documented use of at least 1 dose of double blind test article were included in the safety population. Subjects who were dispensed test article but had no documented use of at least 1 dose were not being included in the safety population.

Statistical Methods:

The primary endpoint was tested at the $\alpha = 0.05$ level, 2-sided. All other reported p-values were presented as descriptive statistics, and thus no adjustment for multiple comparisons was made.

This study was designed to test the superiority of etanercept 50 mg administered once weekly compared with SSZ 3 g administered daily based on a primary endpoint of 20% improvement in ASAS response criteria (ASAS 20) at Week 16. The null hypothesis was that there was no difference in the ASAS 20 response at Week 16 between the 2 treatment groups.

If a subject had a missing evaluation for any 1 of the 4 AS domains, the subject was considered a nonresponder at that time point.

The primary endpoint, 20 % improvement in ASAS response criteria (ASAS 20), was analyzed using a chi-square test (Cochran-Mantel-Haenszel analysis of variance [ANOVA] test), stratified by site (or region whichever more appropriate, based on site sizes). The value used was the Week 16 visit; for subjects who discontinued before Week 16, the last evaluation after baseline and prior to discontinuation was used (last observation carried forward [LOCF]).

Response variables for secondary endpoints were analyzed using the same approach as for the primary endpoint. For continuous scores, the change from baseline to each scheduled visit for both observed cases (OC) and LOCF were analyzed using an analysis of covariance (ANCOVA) model with the terms of treatment, center, and baseline score.

The primary hypothesis of equal ASAS 20 response rates at 16 weeks in the 2 treatment groups was tested using the Fisher exact test.

Efficacy analyses used the LOCF approach for missing data imputation; OC results were also presented for each visit.

The mean changes from baseline for the 4 AS assessment domains were summarized, and statistical tests were conducted for the comparisons between treatment groups.

All randomized subjects with documented use of at least 1 dose of double blind study drug were included in the safety population.

For continuous health outcome, safety, and secondary efficacy parameters, 1-way ANOVA or ANCOVA models were used, with treatment group and pooled site as a factor and baseline measurement as a covariate for comparisons among treatment groups. For dichotomous health outcomes, safety, and secondary efficacy endpoints, Fisher exact test or Chi-square test was used.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition and subjects analyzed is provided in Table 2.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Etanercept	Sulphasalazine	Total
Assigned to study treatment	379	187	566
Completed	353 (93.1)	168 (89.8)	521 (92.0)
Withdrawals[a]	26 (6.9)	19 (10.2)	45 (8.0)
Adverse event	15 (4.0)	12 (6.4)	27 (4.8)
Lost to follow-up	3 (0.8)	1 (0.5)	4 (0.7)
Other	0	1 (0.5)	1 (0.2)
Protocol violation	1 (0.3)	1 (0.5)	2 (0.4)
Subject request	3 (0.8)	2 (1.1)	5 (0.9)
Unsatisfactory response - efficacy	4 (1.1)	2 (1.1)	6 (1.1)
Analyzed for efficacy	379 (100)	187 (100)	566 (100)
Analyzed for safety			
Adverse events	379 (100)	187 (100)	566 (100)
Laboratory data	379 (100)	187 (100)	566 (100)

a. Total withdrawn was the sum of individual reasons because they were mutually exclusive by subject.

Demographic characteristics for the 566 subjects who enrolled in the study are summarized in Table 3. The population was predominately male and white, with a mean age of 40.76 years. No significant differences were noted between the treatment groups.

Table 3. Demographic Characteristics - ITT Population

Characteristic	p-Value	Treatment		
		Etanercept (N=379)	Sulphasalazine (N=187)	Total (N=566)
Age (year)				
n		379	187	566
Mean	0.843[a]	40.69	40.90	40.76
Standard deviation		11.69	12.23	11.86
Sex,	0.839[b]			
Female		100 (26.39)	47 (25.13)	147 (25.97)
Male		279 (73.61)	140 (74.87)	419 (74.03)
Ethnic origin	0.972[b]			
Arabic		6 (1.58)	3 (1.60)	9 (1.59)
Asian		18 (4.75)	10 (5.35)	28 (4.95)
Black or African American		2 (0.53)	0	2 (0.35)
Other		22 (5.80)	12 (6.42)	34 (6.01)
White		331 (87.34)	162 (86.63)	493 (87.10)
Baseline height (cm)				
N		377	186	563
Mean	0.640[a]	172.33	171.93	172.20
Standard deviation		9.92	8.39	9.43
Baseline weight (kg)				
N		377	186	563
Mean	0.224[a]	79.01	77.33	78.46
Standard deviation		15.72	14.75	15.41
Body Mass Index (kg/m^2)				
N		377	186	563
Mean	0.223[a]	26.58	26.08	26.41
Standard deviation		4.71	4.25	4.57

ITT = intent to treat; N = number of subjects in specific group; n = number of subjects with specified criteria.
a. One-way analysis of variance with treatment as a factor.
b. Fisher exact test p-value (2-tail).

Efficacy and Outcome Research Results:

Primary Endpoint Result:

Proportion of Subjects Who Achieved ASAS 20 at Week 16:

The proportions of subjects who achieved ASAS 20 response at Week 16 in the etanercept and SSZ groups are presented in Table 4 (LOCF and observed data analysis). Significantly more etanercept-treated subjects than SSZ-treated subjects achieved ASAS 20 at Week 16 (75.93% versus 52.94%; p<0.001).

Table 4. Number (%) of Subjects Who Achieved ASAS 20 at Week 16

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) Subjects Who Achieved ASAS 20 (LOCF)			
Week 16	287/378 (75.93%)	99/187 (52.94%)	<.001
Number (%) Subjects Who Achieved ASAS 20 (Observed)			
Week 16	278/353 (78.75%)	94/167 (56.29%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Secondary Endpoints Results:

Proportion of Subjects Who Achieved ASAS 20 at Time Points Other Than Week 16:

The proportions of subjects who achieved ASAS 20 response at time points other than Week 16 in the etanercept and SSZ groups are presented in Table 5 (LOCF and observed data analysis). Analyses for ASAS 20 response other than Week 16 revealed that the proportion of subjects who achieved ASAS 20 was higher at Week 2 through 12 in the etanercept group compared with the SSZ group; the difference was significant ($p<0.001$) at all other time points.

Table 5. Number (%) of Subjects Who Achieved ASAS 20 at Week 2 Through 12

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved ASAS 20 (LOCF)			
Week 2	203/375 (54.13%)	52/185 (28.11%)	<.001
Week 4	241/377 (63.93%)	79/187 (42.25%)	<.001
Week 8	277/378 (73.28%)	92/187 (49.20%)	<.001
Week 12	268/378 (70.90%)	98/187 (52.41%)	<.001
Number (%) of Subjects Who Achieved ASAS 20 (Observed)			
Week 2	203/375 (54.13%)	52/185 (28.11%)	<.001
Week 4	239/373 (64.08%)	77/184 (41.85%)	<.001
Week 8	273/363 (75.21%)	89/176 (50.57%)	<.001
Week 12	261/362 (72.10%)	94/176 (53.41%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects Who Achieved ASAS 40 at Week 16 (and at Other Time Points):

The LOCF and OC analysis of subjects who achieved an ASAS 40 response at Week 2 through 16 is presented in Table 6. The proportion of subjects who achieved ASAS 40 was significantly ($p<0.001$) higher in the etanercept group compared with the SSZ group at Week 2 through 16. Overall, the greatest percentage of subjects who achieved ASAS 40 occurred at Week 16 in the etanercept (59.79%) and SSZ (32.62%) treatment groups.

Table 6. Number (%) of Subjects Who Achieved ASAS 40

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved ASAS 40 (LOCF)			
Week 2	127/375 (33.87%)	20/185 (10.81%)	<.001
Week 4	159/377 (42.18%)	39/187 (20.86%)	<.001
Week 8	206/378 (54.50%)	56/187 (29.95%)	<.001
Week 12	220/378 (58.20%)	63/187 (33.69%)	<.001
Week 16	226/378 (59.79%)	61/187 (32.62%)	<.001
Number (%) of Subjects Who Achieved ASAS 40 (Observed)			
Week 2	127/375(33.87%)	20/185(10.81%)	<.001
Week 4	157/373(42.09%)	38/184(20.65%)	<.001
Week 8	203/363(55.92%)	55/176(31.25%)	<.001
Week 12	215/362(59.39%)	61/176(34.66%)	<.001
Week 16	219/353(62.04%)	59/167(35.33%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects Who Achieved ASAS 50 at Week 16 (and at Other Time Points):

The proportion of subjects who achieved ASAS 50 response at Week 2 through 16 is summarized in Table 7. The proportion of subjects who achieved ASAS 50 was significantly ($p<0.001$) higher in the etanercept group compared with the SSZ group at Week 2 through 16. Overall, the greatest percentage of subjects who achieved ASAS 50 occurred at Week 16 in the etanercept (56.61%) and SSZ (32.09%) treatment groups.

Table 7. Number (%) of Subjects Who Achieved ASAS 50

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved ASAS 50 (LOCF)			
Week 2	113/375 (30.13%)	14/185 (7.57%)	<.001
Week 4	148/377 (39.26%)	36/187 (19.25%)	<.001
Week 8	183/378 (48.41%)	50/187 (26.74%)	<.001
Week 12	209/378 (55.29%)	56/187 (29.95%)	<.001
Week 16	214/378 (56.61%)	60/187 (32.09%)	<.001
Number (%) of of Subjects Who Achieved ASAS 50 (Observed)			
Week 2	113/375 (30.13%)	14/185 (7.57%)	<.001
Week 4	146/373 (39.14%)	35/184 (19.02%)	<.001
Week 8	180/363 (49.59%)	49/176 (27.84%)	<.001
Week 12	205/362 (56.63%)	54/176 (30.68%)	<.001
Week 16	207/353 (58.64%)	58/167 (34.73%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects Who Achieved ASAS 70 at Week 16 (and at Other Time Points):

The proportion of subjects who achieved ASAS 70 response at Week 2 through 16 is summarized in Table 8. The proportion of subjects who achieved ASAS 70 was significantly ($p<0.001$) higher in the etanercept group compared with the SSZ group at Week 2 through 16. Overall, the greatest percentage of subjects who achieved ASAS 70 occurred at Week 16 in the etanercept (38.36%) and SSZ (20.86%) treatment groups.

Table 8. Number (%) of Subjects Who Achieved ASAS 70

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved ASAS 70 (LOCF)			
ASAS 70 response			
Week 2	57/375 (15.20%)	7/185 (3.78%)	<.001
Week 4	88/377 (23.34%)	16/187 (8.56%)	<.001
Week 8	118/378 (31.22%)	21/187 (11.23%)	<.001
Week 12	137/378 (36.24%)	29/187 (15.51%)	<.001
Week 16	145/378 (38.36%)	39/187 (20.86%)	<.001
Number (%) of of Subjects Who Achieved ASAS 70 (Observed)			
Week 2	57/375 (15.20%)	7/185 (3.78%)	<.001
Week 4	88/373 (23.59%)	15/184 (8.15%)	<.001
Week 8	117/363 (32.23%)	20/176 (11.36%)	<.001
Week 12	136/362 (37.57%)	28/176 (15.91%)	<.001
Week 16	142/353 (40.23%)	38/167 (22.75%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects Who Achieved ASAS 5/6 at Week 16 (and at Other Time Points):

The proportions of subjects who achieved ASAS 5/6 response at Week 2 through 16 is summarized in Table 9. The proportion of subjects who achieved ASAS 5/6 was significantly ($p<0.001$) higher in the etanercept group compared with the SSZ group at Week 2 through 16. Overall, the greatest percentage of subjects who achieved ASAS 5/6 occurred at Week 12 in the etanercept (45.48%) and SSZ (21.23%) treatment groups.

Table 9. Number (%) of Subjects Who Achieved ASAS 5/6

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved ASAS 5/6 (LOCF)			
Week 2	109/352 (30.97%)	15/172 (8.72%)	<.001
Week 4	143/361 (39.61%)	25/179 (13.97%)	<.001
Week 8	167/364 (45.88%)	33/179 (18.44%)	<.001
Week 12	172/364 (47.25%)	40/179 (22.35%)	<.001
Week 16	166/365 (45.48%)	38/179 (21.23%)	<.001
Number (%) of Subjects Who Achieved ASAS 5/6 (Observed)			
Week 2	109/352 (30.97%)	15/172 (8.72%)	<.001
Week 4	141/348 (40.52%)	24/174 (13.79%)	<.001
Week 8	159/338 (47.04%)	32/165 (19.39%)	<.001
Week 12	163/338 (48.22%)	39/164 (23.78%)	<.001
Week 16	155/332 (46.69%)	38/158 (24.05%)	<.001

ASAS = Assessment of Ankylosing Spondylitis; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Change From Baseline by Visit in theVAS Patient Global Assessments:

Patient Global Assessment of Disease Activity VAS was measured on a 0 to 100 mm scale, with 0 = no disease activity. Overall, mean scores decreased in both treatment groups from Week 2 through 16 (Table 10). The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Mean Patient Global Assessment of Disease Activity VAS scores for peripheral joint arthritis decreased in both treatment groups from Week 2 through 16 (Table 10). The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points. The data are presented only for those subjects who had a tender or swollen joint count of >0 at baseline.

Table 10. Mean Patient Global Assessment - VAS (% Change From Baseline): LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean Patient Global Assessment of Disease Activity VAS (% Change From Baseline)			
Baseline	65.21 (0.00)	65.57 (0.00)	0.816
Week 2	41.98 (35.70)	53.35 (18.46)	<0.001
Week 4	37.82 (42.02)	48.76 (25.62)	<0.001
Week 8	33.92 (47.98)	46.60 (28.93)	<0.001
Week 12	31.13 (52.26)	44.59 (31.98)	<0.001
Week 16	29.61 (54.61)	44.87 (31.57)	<0.001
Mean Patient Global Assessment of Peripheral Joint Arthritis VAS (% Change From Baseline)			
Baseline	51.88 (0.00)	51.83 (0.00)	0.978
Week 2	35.63 (32.02)	46.98 (9.91)	<0.001
Week 4	31.21 (40.67)	42.11 (20.05)	<0.001
Week 8	27.26 (48.17)	39.34 (24.77)	<0.001
Week 12	25.64 (51.24)	37.24 (28.77)	<0.001
Week 16	23.30 (55.60)	37.27 (28.63)	<0.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each treatment group; VAS = Visual Analog Scale.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Change From Baseline by Visit in the VAS Physician Global Assessments:

Physician Global Assessment of Disease Activity VAS was measured on a 0 to 100 mm scale, with 0 indicating no disease activity. Overall, mean scores in both treatment groups decreased from Week 2 through 16 (Table 11). The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Physician Global Assessment VAS for peripheral joint arthritis also showed a decrease in mean scores in both treatment groups from Week 2 through 16 (Table 11). The mean percentage change from baseline was significantly greater in the etanercept group compared with the SSZ group at all time points.

Table 11. Mean Physician Global Assessment – VAS (% Change From Baseline): LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean Physician Global Assessment of Disease Activity VAS (% Change From Baseline)			
Baseline	60.08 (0.00)	60.07 (0.00)	0.979
Week 2	38.25 (36.44)	48.48 (19.39)	<0.001
Week 4	31.64 (47.34)	42.25 (29.68)	<0.001
Week 8	26.87 (55.29)	38.97 (35.14)	<0.001
Week 12	23.68 (60.60)	37.16 (38.16)	<0.001
Week 16	22.37 (62.77)	34.56 (42.48)	<0.001
Mean Physician Global Assessment of Peripheral Joint Arthritis VAS (% Change From Baseline)			
Baseline	35.07 (0.00)	34.77 (0.00)	0.968
Week 2	21.69 (39.46)	29.68 (16.89)	<0.001
Week 4	18.02 (49.65)	23.23 (34.27)	0.006
Week 8	15.21 (57.50)	21.67 (38.10)	<0.001
Week 12	13.20 (63.12)	21.27 (39.25)	<0.001
Week 16	11.82 (66.87)	20.71 (40.90)	<0.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each treatment group; VAS = Visual Analog Scale.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Change From Baseline by Visit in the VAS Assessment of Nocturnal and Total Back Pain:

The mean scores and percentage changes from baseline at Week 2 through 16 for the Nocturnal Back Pain Assessment and Total Back Pain Assessment VAS are summarized in Table 12.

Nocturnal Back Pain was measured on a 0 to 100 mm VAS scale, with 0 indicating no pain. Overall, mean scores decreased in both treatment groups at Week 2 through 16 compared with baseline. The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Total Back Pain was measured on a 0 to 100 mm VAS scale, with 0 indicating no pain. Overall, mean scores decreased in both treatment groups from Week 2 through 16. The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Table 12. Mean Total Back Pain and Mean Nocturnal Back Pain VAS (% Change From Baseline): LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean Nocturnal Back Pain VAS (% Change From Baseline)			
Baseline	63.35 (0.00)	63.19 (0.00)	0.934
Week 2	37.08 (41.66)	51.09 (18.98)	<.001
Week 4	31.67 (50.09)	44.79 (29.13)	<.001
Week 8	27.92 (55.91)	41.54 (34.26)	<.001
Week 12	26.56 (58.06)	39.46 (37.55)	<.001
Week 16	25.42 (59.86)	41.19 (34.83)	<.001
Mean Total Back Pain VAS (% Change From Baseline)			
Baseline	63.09 (0.00)	61.61 (0.00)	0.424
Week 2	39.07 (38.17)	51.88 (15.68)	<0.001
Week 4	35.10 (44.37)	45.14 (26.73)	<0.001
Week 8	31.04 (50.82)	43.95 (28.68)	<0.001
Week 12	29.87 (52.65)	41.51 (32.62)	<0.001
Week 16	28.00 (55.63)	41.91 (31.98)	<0.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each treatment group; VAS = Visual Analog Scale.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Change From Baseline by Visit in BASFI and its Components:

The mean scores and percentage change from baseline at Week 2 through 16 for the BASFI VAS (0-100 mm) are summarized in Table 13. Overall, mean scores decreased in both treatment groups at Week 2 through 16 compared with baseline. The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Table 13. Mean BASFI VAS (% Change From Baseline)

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean BASFI VAS (% Change From Baseline): LOCF			
Baseline	55.04 (0.00)	55.05 (0.00)	0.982
Week 2	40.46 (26.70)	47.88 (13.02)	<.001
Week 4	35.98 (34.70)	44.04 (20.00)	<.001
Week 8	31.78 (42.26)	41.59 (24.45)	<.001
Week 12	30.11 (45.31)	40.40 (26.61)	<.001
Week 16	28.72 (47.84)	39.35 (28.52)	<.001
Mean Score (% Change From Baseline) for BASFI (Observed)			
Baseline	55.04 (0.00)	55.05 (0.00)	0.982
Week 2	40.46 (26.70)	47.88 (13.02)	<.001
Week 4	35.92 (34.63)	44.20 (19.77)	<.001
Week 8	30.97 (43.41)	41.54 (24.84)	<.001
Week 12	29.36 (46.38)	40.39 (27.12)	<.001
Week 16	27.52 (49.81)	37.80 (31.81)	<.001

ANCOVA = analysis of covariance; BASFI = Bath Ankylosing Spondylitis Functional Index; N = number of subjects in each treatment group; LOCF = last observation carried forward; VAS = Visual Analog Scale.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Change From Baseline by Visit in BASDAI and its Components:

The mean scores and percentage change from baseline at Week 2 through 16 for BASDAI are shown in Table 14. Overall, mean scores decreased in both treatment groups at Week 2 through 16 compared with baseline. The mean percentage change from baseline was significantly ($p<0.001$) greater in the etanercept group compared with the SSZ group at all time points.

Table 14. Mean BASDAI (% Change From Baseline)

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean BASDAI (% Change From Baseline): LOCF			
Baseline	59.27 (0.00)	59.14 (0.00)	0.950
Week 2	38.85 (34.53)	50.68 (14.10)	<.001
Week 4	34.14 (42.40)	44.40 (24.92)	<.001
Week 8	30.44 (48.64)	41.52 (29.81)	<.001
Week 12	28.12 (52.56)	40.30 (31.87)	<.001
Week 16	27.24 (54.06)	39.41 (33.38)	<.001
Mean Score (% Change From Baseline) for BASDAI (Observed)			
Baseline	59.27 (0.00)	59.14 (0.00)	0.950
Week 2	38.85 (34.53)	50.68 (14.10)	<.001
Week 4	34.05 (42.46)	44.27 (25.19)	<.001
Week 8	29.45 (50.02)	41.06 (30.37)	<.001
Week 12	27.12 (53.99)	39.95 (32.41)	<.001
Week 16	25.68 (56.42)	37.87 (35.90)	<.001

ANCOVA = analysis of covariance; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; N = number of subjects in each treatment group; LOCF = last observation carried forward; VAS = Visual Analog Scale.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Proportion of Subjects Who Achieved a 50% Improvement in BASDAI by Visit:

The proportions of subjects who achieved a 50% improvement in BASDAI at Week 2 through 16 are presented in Table 15. A significantly ($p<0.001$) greater proportion of subjects in the etanercept group achieved 50% improvement compared with the SSZ group at Week 2 through 16.

Table 15. Number (%) of Subjects Who Achieved a 50% Improvement in BASDAI: LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Week 2	126/376 (33.51%)	20/185 (10.81%)	<.001
Week 4	165/378 (43.65%)	41/187 (21.93%)	<.001
Week 8	200/379 (52.77%)	59/187 (31.55%)	<.001
Week 12	220/379 (58.05%)	70/187 (37.43%)	<.001
Week 16	239/379 (63.06%)	71/187 (37.97%)	<.001

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Change From Baseline by Visit in the Complete Joint Assessment (70 joints):

The mean joint count and the percentage change from baseline at Week 2 through 16 for the Tender Joint Count and Swollen Joint Count in subjects with a baseline count >0 are summarized in Table 16.

The mean Tender Joint count decreased at most weeks compared with baseline in the etanercept and SSZ treatment groups. Subjects in the etanercept group had 52% improvement in tender joint count from baseline at Week 16 versus 33% in the SSZ group.

The mean Swollen Joint counts decreased at most weeks compared with baseline in the etanercept and SSZ treatment groups. Subjects in the etanercept group had 61% improvement in swollen joint count from baseline at Week 16 versus 20% in the SSZ group.

Table 16. Mean Joint Count in Subjects With Baseline >0 (% Change From Baseline): LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean Tender Joint Count in Subjects With Baseline >0 (% Change in Baseline): LOCF			
Baseline	6.52 (0.00)	6.36 (0.00)	0.949
Week 2	4.91(25.27)	4.88 (22.78)	0.760
Week 4	4.02 (38.53)	4.62 (27.36)	0.151
Week 8	3.70 (43.25)	4.66 (26.57)	0.040
Week 12	3.76 (42.33)	4.23 (33.49)	0.216
Week 16	3.11 (52.15)	4.26 (33.02)	0.019
Mean Swollen Joint Count in Subjects With Baseline > 0 (% Change From Baseline): LOCF			
Baseline	3.42 (0.00)	3.52 (0.00)	0.642
Week 2	2.22 (35.28)	2.42 (31.74)	0.702
Week 4	1.94 (43.57)	2.57 (26.99)	0.162
Week 8	1.96 (42.69)	2.67 (24.15)	0.124
Week 12	1.62 (52.63)	2.90 (17.61)	0.037
Week 16	1.33 (61.11)	2.82 (19.89)	0.037

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Frequency and Time to Partial Remission:

Partial remission was achieved at Week 16 by 33.25% of subjects in the etanercept group compared with 15.51% of subjects in the SSZ group (Table 17). Overall, a significantly ($p<0.001$) greater proportion of subjects achieved partial remission at Week 2 through 16 in the etanercept treatment group compared with the SSZ group.

Table 17. Number (%) of Subjects Who Achieved Partial Remission

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Number (%) of Subjects Who Achieved Partial Remission (LOCF)			
Week 2	44/376 (11.70%)	6/185 (3.24%)	0.001
Week 4	69/378 (18.25%)	13/187 (6.95%)	<.001
Week 8	100/379 (26.39%)	22/187 (11.76%)	<.001
Week 12	118/379 (31.13%)	26/187 (13.90%)	<.001
Week 16	126/379 (33.25%)	29/187 (15.51%)	<.001
Number (%) of (Proportion) of Subjects Who Achieved Partial Remission (Observed)			
Week 2	44/376(11.70%)	6/185 (3.24%)	0.001
Week 4	69/374(18.45%)	13/184 (7.07%)	<.001
Week 8	99/364(27.20%)	22/176 (12.50%)	<.001
Week 12	117/363(32.23%)	26/176 (14.77%)	<.001
Week 16	123/354(34.75%)	29/167 (17.37%)	<.001

LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

The 25th percentile of time to remission (estimated timepoint at which 25% of subjects have experienced remission) was 57 days in the etanercept group and 115 days in the SSZ group, based on Kaplan-Meier estimates (Table 18).

Table 18. Time to Achieve Partial Remission (Observed)

Survival Statistics	Time to Response Etanercept	Time to Response Sulphasalazine
Kaplan-Meier 25th percentile (95% CI)	57 (30,58)	115 (113,-[a])
Kaplan-Meier median (95% CI)	- (116,-)	-
Kaplan-Meier 75th percentile (95% CI)	-	-
Kaplan-Meier estimate of probability of response at Week 16 (95% CI)	48.4% (40.0%, 57.4%)	28.2% (19.1%, 40.3%)

p ≤0001 (obtained from log-rank statistics of Kaplan-Meier survival model). Censored at 118 days.
CI = confidence interval.
a. Could not be calculated (median and 75th percentiles were not observed).

Change From Baseline by Visit in the Spinal Mobility:

The mean percentage change from baseline for total BASMI score was significantly ($p<0.001$) greater in the etanercept treatment group than in the SSZ treatment group at all time points (Table 19).

The mean measurements in cervical rotation (cm) increased in both treatment groups compared with baseline at all time points (Table 19). Overall, the mean percentage change from baseline was significantly greater in the etanercept treatment group compared to the SSZ treatment group at all post-baseline time points.

Mean intermalleolar distance (cm) increased at all time points in the etanercept group and at most time points in the SSZ group compared with baseline (Table 19). Overall, the percentage change from baseline was significantly higher in the etanercept group compared with the SSZ group at all post-baseline time points.

Mean modified Schober's test measurements increased at all time points in both treatment groups compared with baseline (Table 19). Overall, the mean percentage change from

baseline was significantly greater in the etanercept treatment group compared to the SSZ treatment group at all post-baseline time points.

Mean lateral side flexion measurements (cm) increased in both treatment groups compared with baseline (Table 19). The percent change from baseline was significantly higher at Week 16 in the etanercept group compared with the SSZ group.

The mean measurements (cm) and percent change from baseline for the tragus-to-wall assessment is shown in Table 19. The percent change from baseline was significantly greater in the etanercept group compared with the SSZ group at Week 8 only.

The mean score and the percent change in baseline at Week 2 through 16 for the occiput-to-wall distance assessment is shown in Table 19. Mean scores decreased in both treatment groups at Week 2 through 16 compared with baseline. The percent change from baseline was significantly ($p<0.05$) higher at Week 4, 8, and 12 in the etanercept group compared with the SSZ group.

A significantly ($p<0.05$) greater proportion of subjects had no worsening in the occiput-to-wall distance assessment at Week 2, 8, and 16 in the etanercept treatment group compared with the SSZ treatment group (Table 19). The greatest proportion of subjects with no worsening in occiput-to-wall distance assessment occurred at Week 4 in both treatment groups.

The mean measurement and the percent change from baseline at Week 2 through 16 for the chest expansion assessment are summarized in Table 19 (a small number of subjects were excluded from this analysis because the chest expansion data were not evaluable). Change from baseline increased at Week 4 through 16 in the etanercept group and at Week 8 through 16 in the SSZ group and was greater in the etanercept group compared with the SSZ group at Week 8 through 16. However, no significant differences were noted between treatment groups.

Table 19. Assessments of Spinal Mobility

	Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Mean BASMI (% change from Baseline): LOCF	Baseline	3.70 (0.00)	3.43 (0.00)	0.167
	Week 2	3.19 (14.05)	3.40 (2.31)	<0.001
	Week 4	3.07 (17.79)	3.29 (4.66)	<0.001
	Week 8	2.91(22.10)	3.21 (7.00)	<0.001
	Week 12	2.82 (24.53)	3.14 (9.62)	<0.001
	Week 16	2.78 (25.61)	3.21 (7.87)	<0.001
Mean measurements (cm) for cervical rotation (% change from Baseline): LOCF	Baseline	54.60 (0.00)	56.29 (0.00)	0.362
	Week 2	58.74 (7.76)	58.20 (3.63)	0.018
	Week 4	60.92 (11.58)	59.83 (6.29)	0.008
	Week 8	61.85 (13.28)	60.44 (7.37)	0.007
	Week 12	62.77 (14.96)	61.32 (9.27)	0.017
	Week 16	63.41 (16.15)	61.66 (9.86)	0.012
Mean measurements (cm) for intermalleolar distance (% change from Baseline): LOCF	Baseline	91.80 (0.00)	91.51 (0.00)	0.910
	Week 2	95.37 (3.95)	91.18 (-0.01)	0.010
	Week 4	97.49 (6.27)	93.12 (1.76)	0.003
	Week 8	99.32 (8.19)	95.35 (4.20)	0.005
	Week 12	99.05 (7.90)	94.96 (3.94)	0.015
	Week 16	99.85 (8.77)	94.48 (3.41)	<0.001
Mean measurement for the modified schober's test (% change from Baseline): LOCF	Baseline	3.69 (0.00)	3.84 (0.00)	0.418
	Week 2	4.15 (13.39)	3.90 (2.36)	0.003
	Week 4	4.19 (15.03)	3.95 (3.39)	<0.001
	Week 8	4.40 (20.44)	4.07 (6.77)	0.001
	Week 12	4.42 (20.44)	4.24 (11.20)	0.038
	Week 16	4.38 (19.62)	4.05 (5.99)	0.002
Mean measurements for lateral side flexion (% change from Baseline): LOCF	Baseline	10.13 (0.00)	10.25 (0.00)	0.772
	Week 2	10.91 (7.81)	10.58 (3.22)	0.139
	Week 4	11.07 (9.39)	10.86 (5.95)	0.306
	Week 8	11.32 (11.75)	10.88 (6.15)	0.095
	Week 12	11.51 (13.62)	10.99 (7.12)	0.058
	Week 16	11.48 (13.33)	10.82 (5.56)	0.022
Mean measurements for tragus-to-wall (% change from Baseline): LOCF	Baseline	15.59 (0.00)	15.22 (0.00)	0.427
	Week 2	15.17 (2.51)	15.08 (1.11)	0.219
	Week 4	15.11 (3.14)	15.00 (1.45)	0.184
	Week 8	15.00 (3.85)	15.06 (1.05)	0.037
	Week 12	15.14 (3.01)	14.90 (2.10)	0.640
	Week 16	14.93 (4.23)	14.94 (1.77)	0.075
Mean occiput-to-wall distance (% change from Baseline): LOCF	Baseline	5.99 (0.00)	5.55 (0.00)	0.418
	Week 2	5.52 (7.54)	5.50 (1.96)	0.054
	Week 4	5.28 (12.00)	5.54 (0.18)	0.002
	Week 8	5.13 (14.19)	5.54 (0.18)	<0.001
	Week 12	5.09 (15.03)	5.22 (5.95)	0.012
	Week 16	5.32 (11.19)	5.33 (3.96)	0.333
Mean chest expansion (% change from Baseline): LOCF	Baseline	4.28 (0.00)	4.42 (0.00)	0.721
	Week 2	4.26 (2.39)	4.25 (-3.18)	0.723
	Week 4	4.40 (7.00)	4.33 (-1.36)	0.577
	Week 8	4.45 (8.47)	4.48 (1.36)	0.800
	Week 12	4.61 (12.35)	4.56 (2.71)	0.485
	Week 16	4.68 (14.29)	4.48 (1.81)	0.349

ANCOVA = analysis of covariance; BASMI = Bath Ankylosing Spondylitis Metrology Index; LOCF = last observation carried forward; N = number of subjects in each group.

a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Proportion of Subjects With Evaluation <20 (on a Scale of 0 to 100 mm) in VAS Patient Global Assessment:

Subjects with a Patient Global Assessment of Disease Activity VAS of <20 (0-100 mm scale) at Week 2 through 16 are summarized in Table 20. The percentage of subjects with evaluations of <20 increased in both treatment groups but was significantly higher in the etanercept compared with the SSZ group at all time points.

Table 20. Number (%) of Subjects With Evaluation <20 (Scale of 0-100) in Patient Global Assessment of Disease Activity VAS: LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Week 2	76/376 (20.21)	21/185 (11.35)	0.009
Week 4	113/378 (29.89)	29/187 (15.51)	<0.001
Week 8	128/379 (33.77)	35/187 (18.72)	<0.001
Week 12	167/379 (44.06)	37/187 (19.79)	<0.001
Week 16	166/379 (43.80)	46/187 (24.60)	<0.001

LOCF = last observation carried forward; N = number of subjects in each treatment group; VAS = Visual Analog Scale.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects With Evaluation <20 (on a Scale of 0 to 100 mm) in VAS Pain Score Represented by the Average of VAS Total and Nocturnal Pain Scores:

The number and percentage of subjects with total and nocturnal back pain VAS scores of <20 at Week 2 through 16 are summarized in Table 21. The proportion of subjects with scores <20 increased in both groups compared with baseline at all time points; however, a significantly ($p<0.001$) higher proportion of subjects were noted in the etanercept group compared with the SSZ group at all time points.

Table 21. Number (%) of Subjects With Evaluation <20 (Scale of 0-100) in Average of Total and Nocturnal Back Pain VAS: LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Week 2	109/376 (28.99)	23/185 (12.43)	<0.001
Week 4	142/378 (37.57)	35/187 (18.72)	<0.001
Week 8	166/379 (43.80)	45/187 (24.06)	<0.001
Week 12	182/379 (48.02)	49/187 (26.20)	<0.001
Week 16	193/379 (50.92)	52/187 (27.81)	<0.001

LOCF = last observation carried forward; N = number of subjects in each treatment group; VAS = Visual Analog Scale.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects With Evaluation <20 (on a Scale of 0 to 100 mm) in BASFI:

The percentage of subjects with BASFI <20 increased in both groups compared with baseline at all time points; however, a significantly ($p\leq0.001$) higher proportion of subjects were noted in the etanercept group compared with the SSZ group at Week 4 through 16 (Table 22).

Table 22. Number(%) of Subjects With Evaluation <20 (Scale of 0-100) in BASFI: LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Baseline	19/379 (5.01%)	9/187 (4.81%)	0.918
Week 2	94/376 (25.00%)	23/185 (12.43%)	<.001
Week 4	124/378 (32.80%)	37/187 (19.79%)	0.001
Week 8	159/379 (41.95%)	52/187 (27.81%)	0.001
Week 12	162/379 (42.74%)	50/187 (26.74%)	<.001
Week 16	181/379 (47.76%)	56/187 (29.95%)	<.001

BASFI = Bath Ankylosing Spondylitis Functional Index; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Proportion of Subjects With Evaluation <20 (on a Scale of 0 to 100 mm) in BASDAI-2 Morning Stiffness-Related Scores:

The number and percentage of subjects with length of morning stiffness (mean of the last 2 morning stiffness-related BASDAI VAS scores) scores of <20 at Week 2 through 16 are summarized in Table 23. The percentages of subjects with scores of <20 increased in both groups compared with baseline; however, a significantly ($p<0.001$ except for Week 4, $p=0.005$) higher proportion of subjects were noted in the etanercept group compared with the SSZ group at Week 2 through Week 16.

A significantly ($p<0.001$) higher proportion of subjects in the etanercept group compared with the SSZ group had scores of <20 in level of morning stiffness at Week 2 through 16.

Table 23. Number (%) of Subjects With Evaluation <20 (Scale of 0-100) in BASDAI For Length and Level of Morning Stiffness: LOCF

Time on Therapy	Etanercept (N=378)	Sulphasalazine (N=187)	p-Value[a]
Length of Morning Stiffness			
Baseline	19/379 (5.01%)	7/187 (3.74%)	0.498
Week 2	108/376 (28.72%)	26/184 (14.13%)	<.001
Week 4	135/378 (35.71%)	45/187 (24.06%)	0.005
Week 8	160/379 (42.22%)	47/187 (25.13%)	<.001
Week 12	180/379 (47.49%)	54/187 (28.88%)	<.001
Week 16	193/379 (50.92%)	56/187 (29.95%)	<.001
Level of Morning Stiffness			
Baseline	9/379 (2.37%)	1/187 (0.53%)	0.118
Week 2	106/376 (28.19%)	18/185 (9.73%)	<.001
Week 4	136/378 (35.98%)	39/187 (20.86%)	<.001
Week 8	162/379 (42.74%)	48/187 (25.67%)	<.001
Week 12	188/379 (49.60%)	56/187 (29.95%)	<.001
Week 16	196/379 (51.72%)	60/187 (32.09%)	<.001

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; LOCF = last observation carried forward; N = number of subjects in each treatment group.
a. Cochran-Mantel-Haenszel test.

Percentage Change From Baseline for BASDAI Fatigue:

The percentage change from baseline in fatigue, as measured by the BASDAI fatigue VAS, was 47.08% in the etanercept group compared with 26.39% for the SSZ group at Week 16

(Table 24). The etanercept group had a significantly (p<0.001) higher percentage change from baseline compared with the SSZ group at all time points.

Table 24. Mean Score (% Change From Baseline) for BASDAI Fatigue (LOCF)

Time on Therapy	Etanercept (N=379)	Sulphasalazine (N=187)	p-Value[a]
Baseline	61.09 (0.00)	59.90 (0.00)	0.561
Week 2	45.60 (25.47)	54.65 (8.60)	<.001
Week 4	41.09 (32.75)	49.44 (17.46)	<.001
Week 8	36.79 (39.78)	47.29 (21.04)	<.001
Week 12	33.67 (44.88)	45.49 (24.06)	<.001
Week 16	32.32 (47.08)	44.09 (26.39)	<.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each group.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Change From Baseline by Visit in the Acute Phase Reactant Laboratory Assessment of CRP:

At Week 16, mean CRP decreased 62.26% from baseline in the etanercept group compared with a 10.28% decrease in the SSZ group (p<0.001), with significant differences noted between groups beginning at Week 2 (Table 25). Within each treatment group, the change from baseline was significant (p=0.001) at all time points in the etanercept group and was significantly (p<0.05) lower compared with baseline at Weeks 4, 8, 12, and 16 in the SSZ group.

Table 25. Mean C-Reactive-Protein (% Change From Baseline): LOCF

Time on Therapy	Etanercept (N=379)	Sulphasalazine (N=187)	p-Value[a]
Baseline	17.01 (0.00)	15.47 (0.00)	0.346
Week 2	5.87 (65.69)	16.17 (-3.72)	<0.001
Week 4	7.35 (56.88)	13.94 (9.89)	<0.001
Week 8	6.06 (64.32)	14.04 (9.24)	<0.001
Week 12	6.27 (63.08)	13.78 (10.92)	<0.001
Week 16	6.42 (62.26)	13.88 (10.28)	<0.001

ANCOVA = analysis of covariance; LOCF = last observation carried forward; N = number of subjects in each group.
a. ANCOVA model: change = therapy + poolsite (region) + baseline.

Health Outcome Endpoints Results:

Change From Baseline to Week 16 in the EQ-5D:

The percentage change from baseline for the EQ-5D Index score was significantly (p<0.001) higher at Week 16 in the etanercept treatment group (42.86%) compared with the SSZ treatment group (31.82%; Table 26). A significantly (p<0.001) greater proportion of subjects in the etanercept group achieved a meaningful improvement in utility scores as measured by an EQ-5D Index score improvement ≥0.05 (68.88% versus 50.91%).

Table 26. Mean EQ-5D Index Score (% Change From Baseline)

Time on Therapy	Etanercept (N=347)	Sulphasalazine (N=165)	p-Value[a]
Baseline	0.49 (0.00)	0.44 (0.00)	0.093
Week 16	0.70 (42.86)	0.58 (31.82)	<0.001

ANCOVA = analysis of covariance; EQ-5D = EuroQoL-5 Dimensions; N = number of subjects in each group.
a. ANCOVA model: change = baseline score + therapy + poolsite.

The percentage change from baseline in the EQ-5D VAS score was significantly (p<0.001) higher at Week 16 in the etanercept treatment group (36.22%) compared with the SSZ treatment group (24.06%; Table 27). A significantly (p=0.002) greater proportion of subjects in the etanercept group achieved an EQ-5D VAS Score >82 (29.57% versus 17.07%).

Table 27. Mean EQ-5D VAS Score (% Change From Baseline)

Time on Therapy	Etanercept (N=345)	Sulphasalazine (N=164)	p-Value[a]
Baseline	49.67 (0.00)	49.05 (0.00)	0.732
Week 16	67.66 (36.22)	60.85 (24.06)	<0.001

ANCOVA = analysis of covariance; EQ-5D = EuroQoL-5 Dimensions; N = number of subjects in each group; VAS = Visual Analog Scale.
a. ANCOVA model: change = baseline score + therapy + poolsite.

Additionally, for the 5 individual domains of EQ-5D (including Usual Activity Score, Anxiety/Depression Score, Self-Care Score, Pain/Discomfort Score and Mobility Score), the proportion of subjects who reported "no problem" was significantly (p<0.001 for all except pain and discomfort [p=0.002]) higher in the etanercept treatment group versus the SSZ group at Week 16: Usual Activity Score (48.41% versus 29.09%), Anxiety/Depression Score (62.54% versus 46.67%), Self-Care Score (78.10% versus 60.61%), Pain/Discomfort Score (24.21% versus 12.12%) and Mobility Score (60.23% versus 41.82%).

Change From Baseline to Week 16 in the SF-36 and its Domains:

The mean percentage change from baseline in the scores for the SF-36 Physical Component Summary (PCS) was significantly (p<0.001) improved (indicated by a higher score) in the etanercept group compared with the SSZ group (29.59% versus 19.28%; Table 28). The percentage of subjects achieving a meaningful improvement in the SF-36 PCS (PCS score change of ≥5) was significantly (p<0.001) higher in the etanercept group (65.04%) than in the SSZ group (50.00%).

The mean percentage change from baseline in the scores for the SF-36 Mental Component Summary (MCS) was significantly (p<0.001) higher in the etanercept group (11.89%) compared with the SSZ group (3.62%; Table 28). The proportion of subjects with a clinically meaningful improvement in the SF-36 MCS (MCS score change of ≥5) was significantly (p=0.003) higher in the etanercept group (46.99%) versus the SSZ group (32.93%).

The individual domain analysis of SF-36 show that the percent change from baseline was significantly higher in the etanercept group compared with the SSZ group, which indicated more improvement in the etanercept group compared with the SSZ group for all 8 domains.

Table 28. Mean SF-36 Score (% Change From Baseline)

Time on Therapy	Etanercept (N=349)	Sulphasalazine (N=164)	p-Value[a]
Mean SF-36 PCS Score			
Baseline	31.26 (0.00)	30.70 (0.00)	0.449
Week 16	40.51 (29.59)	36.61 (19.28)	<0.001
Mean SF-36 MCS Score			
Baseline	44.14 (0.00)	45.01 (0.00)	0.473
Week 16	49.39 (11.89)	46.64 (3.62)	<0.001

ANCOVA = analysis of covariance; N = number of subjects in each group; MCS = Mental Component Summary; PCS = Physical Component Summary; SF-36 = 36-Item Short-Form Health Survey.
a. ANCOVA model: change = baseline score + therapy + poolsite.

Change From Baseline to Week 16 in the HADS:

The HADS subscales (Anxiety and Depression) scores are as follows: 0 to 7 is normal, 8 to 10 is mild, 11 to 14 is moderate, and 15-21 is severe. Both treatment groups showed improvement in both the HADS Anxiety and Depression scores at Week 16. The mean percentage change from baseline at Week 16 was significantly greater in the etanercept group versus the SSZ group for the Anxiety score (22.31% versus 15.25%, p=0.024; Table 29) and the Depression score (24.73% versus 14.39%; p=0.013; Table 29).

Table 29. Mean HADS Score (% Change From Baseline)

Time on Therapy	Etanercept (N=352)	Sulphasalazine (N=165)	p-Value[a]
Mean HADS Anxiety Score			
Baseline	7.71 (0.00)	8.13 (0.00)	0.273
Week 16	5.99 (22.31)	6.89 (15.25)	0.024
Mean HADS Depression Score			
Baseline	6.43 (0.00)	6.67 (0.00)	0.465
Week 16	4.85 (24.73)	5.70 (14.39)	0.013

ANCOVA = analysis of covariance; HADS = Hospital Anxiety and Depression Scalel; N = number of subjects in each treatment arm.
a. ANCOVA model: change = baseline score + therapy + poolsite.

For the HADS Anxiety subscale, a significantly greater proportion of subjects in the etanercept group than in the SSZ group had scores ≥8 at Week 16 (28.98% versus 43.64%, p<0.001); there was no statistical difference for those with scores ≥11 (15.63% versus 18.79%). For the HADS Depression subscale, a significantly greater proportion of subjects in the etanercept group than in the SSZ group had scores ≥8 (22.73% versus 32.12%, p=0.021); there was no statistical difference for those with scores ≥11 (9.66% versus 11.52%).

Change From Baseline to Week 16 in the ASQoL: The ASQoL was administered only to subjects whose native language was English, Hungarian, and Dutch; therefore not all subjects received this assessment. For the ASQoL, lower scores indicate better function. Greater

improvement was observed at Week 16 in the etanercept group compared with the SSZ group in the ASQoL total score (percentage change from baseline 43.70% versus 19.96%, p=0.010; Table 30).

Table 30. Mean ASQoL Total Score (% Change From Baseline)

Time on Therapy	Etanercept (N=76)	Sulphasalazine (N=34)	p-Value[a]
Baseline	11.03(0.00)	11.32(0.00)	0.719
Week 16	6.21(43.70)	9.06(19.96)	0.010

ANCOVA = analysis of covariance; ASQoL = Ankylosing Spondylitis Quality of Life; N = number of subjects in each group.
a. ANCOVA model: change = baseline score + therapy + poolsite.

Safety Results:

Treatment-Emergent Adverse Events (TEAEs): Non-serious TEAEs (all-causalities) occurring in ≥5% of subjects in either treatment group are summarized in Table 31.

During this study, 1 or more TEAEs were reported by 313 (55.3%) subjects, including 213 (56.2%) subjects in the etanercept group and 100 (53.5%) subjects in the SSZ group. A significantly greater number of subjects in the etanercept group than in the SSZ group reported TEAEs of injection site reaction (10.8% versus 1.6% SSZ; p<0.001). Other common AEs were upper respiratory infection (8.2% etanercept, 9.1% SSZ), headache (7.7% etanercept, 11.2% SSZ), and nausea (6.6% etanercept, 9.6% SSZ).

Table 31. Treatment-Emergent Adverse Events Reported by ≥5% of Subjects in Any Treatment Group by Preferred Terms (All-Causalities)

Body System Adverse Event	Overall p-Value[a]	Treatment		
		Etanercept n=379 n (F)=100 n (M)=279	Sulphasalazine n=187 n (F)=47 n (M)=140	Total n=566 n (F)=147 n (M)=419
Any adverse event	0.590	213 (56.2)	100 (53.5)	313 (55.3)
Body as a whole	0.102	128 (33.8)	50 (26.7)	178 (31.4)
Headache	0.160	29 (7.7)	21 (11.2)	50 (8.8)
Injection site reaction	<0.001[b]	41 (10.8)	3 (1.6)	44 (7.8)
Digestive system	0.249	64 (16.9)	39 (20.9)	103 (18.2)
Nausea	0.237	25 (6.6)	18 (9.6)	43 (7.6)
Respiratory system	0.458	55 (14.5)	32 (17.1)	87 (15.4)
Upper respiratory infection	0.749	31 (8.2)	17 (9.1)	48 (8.5)

Adverse events and serious adverse events are not separated out.
Body system totals are not necessarily the sum of the individual adverse events since a subject could have 2 or more different adverse events in the same body system.
n = total number of subjects; n (F) = number of female subjects; n (M) = number of male subjects
a. Overall p-value by Fisher exact test (2-Tail).
b. Statistical significance at the 0.001 level was denoted by 0.001.

A summary of treatment-related TEAEs reported by ≥5% of subjects in either treatment group is provided in Table 32.

Table 32. Treatment-Emergent Treatment-Related Adverse Events Reported by ≥5% of Subjects in Any Treatment Group by Preferred Terms

Body System Adverse Event	Overall p-Value[a]	Treatment Etanercept n=379 n(F)=100 n(M)=279	Sulphasalazine n=187 n(F)=47 n(M)=140	Total n=566 n(F)=147 n(M)=419
Any adverse event	0.590	113 (29.8)	52 (27.8)	165 (29.2)
Body as a whole	0.102	72 (19.0)	24 (12.8)	96 (17.0)
Headache	0.160	16 (4.2)	15 (8.0)	31 (5.5)
Injection site reaction	<0.001	40 (10.6)	3 (1.6)	43 (7.6)
Digestive system	0.249	35 (9.2)	29 (15.5)	64 (11.3)
Nausea	0.237	19 (5.0)	16 (8.6)	35 (6.2)

Adverse events and serious adverse events are not separated out.
Body system totals are not necessarily the sum of the individual adverse events since a subject could have 2 or more different adverse events in the same body system.
n = total number of subjects; n (F) = number of female subjects; n (M) = number of male subjects
a. Overall p-value by Fisher exact test (2-tail).

Serious Adverse Events: Treatment-emergent SAEs occurring in either treatment group are summarized in Table 33.

Table 33. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Body System Adverse Event	Overall p-Value[a]	Treatment Etanercept n=379	Sulphasalazine n=187	Total n=566
Any adverse event	0.758	7 (1.8)	4 (2.1)	11 (1.9)
Body as a whole	0.109	0	2 (1.1)	2 (0.4)
Abdominal pain	0.330	0	1 (0.5)	1 (0.2)
Accidental injury	0.330	0	1 (0.5)	1 (0.2)
Cardiovascular system	1.000	2 (0.5)	0	2 (0.4)
Migraine	1.000	1 (0.3)	0	1 (0.2)
Supraventricular tachycardia	1.000	1 (0.3)	0	1 (0.2)
Digestive system	0.552	1 (0.3)	1 (0.5)	2 (0.4)
Colitis	1.000	1 (0.3)	0	1 (0.2)
Gastritis	0.330	0	1 (0.5)	1 (0.2)
Musculoskeletal system	1.000	1 (0.3)	0	1 (0.2)
Arthritis	1.000	1 (0.3)	0	1 (0.2)
Nervous system	1.000	4 (1.1)	2 (1.1)	6 (1.1)
Dizziness	0.330	0	1 (0.5)	1 (0.2)
Hypaesthesia[b]	1.000	1 (0.3)	0	1 (0.2)
Neuralgia	1.000	1 (0.3)	0	1 (0.2)
Paresis[b]	1.000	1 (0.3)	0	1 (0.2)
Psychosis	0.330	0	1 (0.5)	1 (0.2)
Ptosis[b]	1.000	1 (0.3)	0	1 (0.2)
Vertigo[b]	1.000	1 (0.3)	0	1 (0.2)

Body system totals are not necessarily the sum of the individual adverse events because a subject could have ≥2 different adverse events in the same body system.
n = total number of subjects.
a. Overall p-value by Fisher exact test (2-tail).
b. Considered to be treatment-related.

Permanent Discontinuations due to Adverse Events: A summary of all-causality AEs leading to permanent discontinuation of subjects is provided in Table 34. The incidence of safety-related withdrawals was lower among subjects in the etanercept group than in the SSZ

group (4.0% versus 6.4%), although this difference was not statistically significant. Overall, the most common TEAEs leading to study withdrawal were rash, nausea, and headache.

Table 34. Number (%) of Subjects With Adverse Events Causing Withdrawal

Body System Adverse Event	Sex	Overall p-Value[a]	Treatment		
			Etanercept n=379 n (M)=279	Sulphasalazine n=187 n (M)=140	Total n=566 n (M)=419
Any adverse event	-	0.212	15 (4.0)	12 (6.4)	27 (4.8)
Body as a whole	-	0.402	3 (0.8)	3 (1.6)	6 (1.1)
Allergic reaction	-	0.330	0	1 (0.5)	1 (0.2)
Asthenia	-	1.000	1 (0.3)	0	1 (0.2)
Chills	-	0.330	0	1 (0.5)	1 (0.2)
Fever	-	0.330	0	1 (0.5)	1 (0.2)
Headache	-	0.602	2 (0.5)	2 (1.1)	4 (0.7)
Injection site reaction	-	1.000	1 (0.3)	0	1 (0.2)
Cardiovascular system	-	0.554	3 (0.8)	0	3 (0.5)
Migraine	-	1.000	2 (0.5)	0	2 (0.4)
Palpitation	-	1.000	1 (0.3)	0	1 (0.2)
Digestive system	-	0.402	3 (0.8)	3 (1.6)	6 (1.1)
Colitis	-	1.000	1 (0.3)	0	1 (0.2)
Diarrhea	-	1.000	2 (0.5)	0	2 (0.4)
Flatulence	-	0.330	0	1 (0.5)	1 (0.2)
Gastroesophageal reflux disease	-	0.330	0	1 (0.5)	1 (0.2)
Nausea	-	0.108	1 (0.3)	3 (1.6)	4 (0.7)
Vomiting	-	0.552	1 (0.3)	1 (0.5)	2 (0.4)
Hemic and lymphatic system	-	0.330	0	1 (0.5)	1 (0.2)
Neutropenia	-	0.330	0	1 (0.5)	1 (0.2)
Metabolic and nutritional	-	1.000	2 (0.5)	0	2 (0.4)
AST/SGOT increased	-	1.000	1 (0.3)	0	1 (0.2)
ALT/SGPT increased	-	1.000	2 (0.5)	0	2 (0.4)
Nervous system	-	0.667	3 (0.8)	2 (1.1)	5 (0.9)
Euphoria	-	0.330	0	1 (0.5)	1 (0.2)
Hypesthesia	-	1.000	1 (0.3)	0	1 (0.2)
Paresis	-	1.000	1 (0.3)	0	1 (0.2)
Psychosis	-	0.330	0	1 (0.5)	1 (0.2)
Vertigo	-	1.000	1 (0.3)	0	1 (0.2)
Respiratory system	-	0.109	0	2 (1.1)	2 (0.4)
Cough increased	-	0.330	0	1 (0.5)	1 (0.2)
Pharyngitis	-	0.330	0	1 (0.5)	1 (0.2)
Voice alteration	-	0.330	0	1 (0.5)	1 (0.2)
Skin and appendages	-	0.123	3 (0.8)	5 (2.7)	8 (1.4)
Alopecia	-	1.000	1 (0.3)	0	1 (0.2)
Eczema	-	0.330	0	1 (0.5)	1 (0.2)
Furunculosis	-	1.000	1 (0.3)	0	1 (0.2)
Herpes zoster	-	0.330	0	1 (0.5)	1 (0.2)
Pruritic rash	-	0.330	0	1 (0.5)	1 (0.2)
Pruritus	-	0.109	0	2 (1.1)	2 (0.4)
Rash	-	1.000	2 (0.5)	1 (0.5)	3 (0.5)
Special senses	-	0.109	0	2 (1.1)	2 (0.4)
Iritis	-	0.330	0	1 (0.5)	1 (0.2)
Taste perversion	-	0.330	0	1 (0.5)	1 (0.2)
Urogenital system	-	1.000	1 (0.3)	0	1 (0.2)
Testis disorder	M	1.000	1 (0.4)	0	1 (0.2)

Body system totals are not necessarily the sum of the individual adverse events since a subject could have 2 or more different adverse events in the same body system. Sex - F, M, or blank indicates the calculation is based on subjects of either female only, male only, or both.
ALT/ SGPT = alanine aminotransferase; AST/ SGOT = asparate aminotransferase; M = male; n = total number of subjects.
a. Overall p-value by Fisher exact test (2-tail).

Death: There were no deaths during this study.

Clinical Laboratory Results: The number and percentage of subjects by treatment group with Grade 3 or 4 laboratory results of potential clinical importance while on therapy are summarized in Table 35.

Table 35. Number (%) of Subjects With Grade 3 or 4 Laboratory Results

Laboratory Parameter Category	Overall p-Value[a]	Treatment		
		Etanercept	Sulphasalazine	Total
Total	0.447	14/379 (3.7)	4/187 (2.1)	18/566 (3.2)
Blood Chemistry				
Sodium mmol/L				
Grade 3	0.330	0/379	1/187 (0.5)	1/566 (0.2)
Total bilirubin µmol/L				
Grade 3	0.034[b]	9/379 (2.4)	0/187	9/566 (1.6)
AST/SGOT mU/mL				
Grade 3	0.552	1/379 (0.3)	1/187 (0.5)	2/566 (0.4)
ALT/SGPT mU/mL				
Grade 3	1.000	1/379 (0.3)	0/187	1/566 (0.2)
Hematology				
Neutrophils 10^9/L				
Grade 3	0.109	0/378	2/187 (1.1)	2/565 (0.4)
Lymphocytes 10^9/L				
Grade 3	1.000	2/378 (0.5)	0/187	2/565 (0.4)
Platelet count 10^9/L				
Grade 4	1.000	1/379 (0.3)	0/187	1/566 (0.2)

For each test, only maximum grade per subject was counted.
ALT/ SGPT = alanine aminotransferase; AST/ SGOT = asparate aminotransferase.
a. Overall p-value by Fisher exact test (2-tail).
b. Statistical significance at the .05 level.

Vital Signs, Physical Findings, and Other Observations Related to Safety: Although there were some statistically significant differences when comparing between groups or within group for changes from baseline in blood pressure and pulse, none of the changes were clinically meaningful. Furthermore, review of the potentially clinically important abnormalities revealed no findings of clinical significance.

CONCLUSIONS:

Overall, the results of this study show that etanercept therapy was superior to SSZ therapy in the treatment of these subjects with AS. There were no unexpected safety findings in this study population.