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

PROTOCOL NO.: 0881A3-102090 (B1801262)

PROTOCOL TITLE: A 12-Week, Randomized, Double-Blind, Multicenter, Pilot Study to Evaluate the Effect of Etanercept 100 mg and 50 mg Weekly in Subjects With Ankylosing Spondylitis

Study Centers: Fifteen centers (15) in Spain took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 13 December 2006 to 06 August 2008

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- To evaluate effect of etanercept (ETN) 100 mg weekly and ETN 50 mg weekly in subjects with ankylosing spondylitis (AS) who failed previous standard therapies.

Secondary Objectives:

- To evaluate the time course of initial treatment response of the 2 ETN treatment regimens.
- To evaluate the effect of the 2 ETN treatment regimens on subject-reported outcomes.
- To evaluate the safety and tolerability profile of the 2 ETN treatment regimens.

METHODS

Study Design: This was a double-blind, randomized, parallel, multicenter pilot study designed to evaluate the efficacy and safety of ETN 100 mg (50 mg twice a week) versus (vs) 50 mg weekly, for 12 weeks, in treatment of adult subjects with AS and previous failure to standard therapies. The group treated with ETN 50 mg weekly also received placebo once a week. The duration of the trial could be for a maximum of 12 weeks. Subjects participated in the trial for up to 18 weeks. The study flow chart is presented in Table 1.

Table 1. Study Flow Chart

Study Week	Screening	Week 0 (Baseline)	Week 2	Week 4 and 8	Week 12 or Early Withdrawal Visit	Follow-Up Visit[a]
Visit Window[b]	**≤6 Weeks**		**±2 Days**	**±3 Days**	**±3 Days**	**15 Days After the Last Dose**
Visit Number	**1**	**2**	**3**	**4 and 5**	**6**	**7**
Study Activity						
Signed informed consent	X					
Medical history	X					
Inclusion/exclusion criteria	X	X				
Adverse events		X	X	X	X	X
Previous/ concomitant medications	X	X	X	X	X	X
Complete physical examination[c]	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X
Complete joint assessment[c]	X	X	X	X	X	
Enthesis pain (MASES index)[c]	X	X	X	X	X	
Global Assessment by Subject[e, c]	X	X	X	X	X	
Global Assessment by Physician[c]	X	X	X	X	X	
Nocturnal and overall spine pain[e,c]	X	X	X	X	X	
BASFI[c]	X	X	X	X	X	
BASDAI[e,c]	X	X	X	X	X	
BASMI[c]	X	X	X	X	X	
Chest expansion[c]	X	X	X	X	X	
Occiput-to-wall distance[c]	X	X	X	X	X	
SF-36	X				X	
Quality of life (Euro Qol)	X				X	X
Pregnancy test[f]	X	X				
Biochemistry/hematology and urine anlysis[c]	X	X		X	X	
CRP[c]	X	X		X	X	
ESR[c]	X	X		X	X	
HLA-B27[g]	X					

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Visit Number	**1**	**2**	**3**	**4 and 5**	**6**	**7**
Study Activity						
Chest X-ray[h]	X					
Sacroiliac X-ray[h]	X					
Randomization and administration of the first dose		X				
Dispensing of study medication		X		X		
Dispensing of subject medication diary		X	X	X		
Dispensing of the scales to be completed by the subject[e]		X	X			
Collection of subject's diary and scales			X	X	X	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BP = blood pressure; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Euro Qol = Ankylosing Spondylitis Quality of Life; HLA-B27 = Human leukocyte antigen B27; MASES index = Masstrich index; PR = pulse rate; SF-36 = 36-Item Short-Form Health Survey.

a. Follow-up telephone call to assess safety approximately 15 days after the last dose.
b. The visits could be scheduled from 2 or 3 days before or after the previous mentioned visit (see flow-chart).
c. Time period between Screening and Baseline visit could not >6 weeks. If this period was >2 weeks, a new test of hematology, biochemistry, urine, CRP and ESR could be performed in the Baseline visit prior to the administration of the first drug dose, in addition to a complete physical examination and the marked scales.
d. Includes sitting BP and PR; weight and height were recorded only at Baseline.
e. Additionally, the participating subjects completed the BASDAI, Global Assessment by the Subject and nocturnal and overall spine pain scales at Weeks 1 and 3.
f. For women of childbearing potential in serum in the Screening visit, and in urine at Baseline visit.
g. Measurement of HLA-B27 could be eliminated if this measurement is previously documented.
h. Waived within 3 months and report was available and included in subject's source documents.

Number of Subjects (Planned and Analyzed): The study was planned to enroll a total of 136 Subjects; 126 subjects were randomized into 2 groups (54 subjects in Group A; 54 subjects in Group B); 108 subjects completed the study.

Diagnosis and Main Criteria for Inclusion and Exclusion: All subjects (aged between 18-70) had to have a diagnosis of AS defined by the modified New York criteria for AS; maintained inflammatory activity for ≥12 weeks defined by:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 (0-10) and at least 1 of the following:
    - Global assessment of the disease by the subject ≥4 (on a scale 0-10);
    - Spinal pain ≥4 on a visual analogue scale (VAS);
    - Increase in erythrocyte sedimentation rate (ESR) and/or CRP above the normality parameters established by the laboratory;
- Arthritis or enthesitis ≥1 site and at least 1 of the following:
    - Global assessment of the disease by the subject ≥4 (On a scale 0-10);
    - Increase in ESR and/or C-reactive protein CRP above the normality parameters established by the laboratory;

And, failure to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) at maximum recommended dose during an overall period of at least 3 months (or a shorter time in case of intolerance, toxicity or contraindication).

Main Criteria for Exclusion: Subjects with a history of contraindications for treatment with anti-tumour necrotic factor (TNF), complete ankylosis of spine, previous treatment with other TNF inhibitors and other biological drugs were excluded from the study.

Study Treatment: Subjects were assigned to 1 of 2 different arms of treatment. One (1) arm with subcutaneous (SC) injections twice weekly for 12 weeks with ETN 50 mg while the other arm with SC injections twice weekly for 12 weeks with ETN 50 mg and placebo in 1 of the weekly administrations. The study medication kit contained the lyophilized injectable study drug and sterile water and was to be kept under refrigerated conditions at 2°C - 8°C and should not have been frozen. Once reconstituted with the sterile water, the study drug was maintained stable for injection for up to 6 hours if kept refrigerated at 2°C - 8°C.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- The primary endpoint was the proportion of subjects who achieved Assessment in Spondylosing Arthritis international Society 20 (ASAS 20) response at Week 12 vs Baseline. This endpoint was derived from the 4 AS assessments (subject global evaluation of disease activity, pain, physical function, and inflammation);

Secondary Efficacy Endpoints:

- Proportion of subjects who achieved ASAS 40, ASAS 50, ASAS 70, ASAS 5/6 responses at Week 12;
- Frequency and time to reach partial remission according;
- Change from Baseline visit and per visit in nocturnal and overall spine pain;
- Change from Baseline visit and per visit inpatient global assessment, and Physician global assessment;
- Change from Baseline visit and per visit in the Bath Ankylosing Spondylitis Functional Index (BASFI) and its independent endpoints, and the BASDAI 50 and its independent endpoints;
- Proportion of subjects who achieve a 50% improvement on the BASDAI per visit;
- Changes from Baseline visit collected in subject's diary of nocturnal and overall spine pain, global assessment by subject and BASDAI weekly during the first 4 weeks;
- Proportion of subjects who achieve ASAS 20, ASAS 40, ASAS 50, ASAS 70, and ASAS 5/6 response according to data collected in each subject's diary;
- Change from Baseline and per visit in spinal mobility (Bath Ankylosing Spondylitis Metrology Index [BASMI], chest expansion and occiput-to-wall distance);
- Changes from Baseline and per visit in complete peripheral joint count;
- Changes from Baseline and per visit in tenderness of enthesis according to Maastrich index (MASES index);
- Changes from Baseline and per visit in CRP and ESR;
- Improvement of ocular inflammatory disease in subjects who had symptoms at Baseline visit;
- Changes in quality of life at 12 weeks vs baseline through the EuroQol (AS Quality of Life) and 36-Item Short-Form Health Survey (SF-36) questionnaires;

Safety Evaluations: Safety evaluations included the results of spontaneously reported signs and symptoms, scheduled physical examinations, vital signs, hematology and chemistry profiles, urine analysis, premature discontinuation and monitoring of all adverse events (AEs), serious adverse events (SAEs).

Statistical Methods:

Analysis Sets:

Intent-to-treat (ITT) population: All randomized subjects who received at least 1 dose of study medication and had at least 1 on therapy evaluation were included in the ITT population used for the statistical efficacy analysis. This ITT population was comprised of 108 subjects (54 for each arm of treatment). This population was analyzed for both efficacy and safety, as they included all subjects who received treatment.

Per protocol (PP) population: All randomized subjects fulfilling the study procedures, lacking major deviations, and having received, at least, 80% of planned treatment injections (≥19) were included in the PP population and analyzed for efficacy (primary endpoint).

This PP population was composed by 87 subjects (43 in Treatment Group A and 44 in Treatment Group B). The efficacy primary endpoint was analyzed in this PP population. The study populations are presented in Table 2.

The safety statistical analysis would be performed on all those randomized subjects who received at least 1 dose of any of the study medications.

Signs test was planned to be used in the case of non-dichotomic ordinal discreet variables, but it has not been finally used, as none variable of this type has been evaluated.

Table 2. Study Populations Sets

Populations	Treatment Group A	Treatment Group B	Total
ITT; N	54 (100)	54 (100)	108 (100)
PP; N	43 (79.62)	44 (81.48)	87 (80.56)

A = 50 mg twice in a week; B = 50 mg once in a week; ITT = intent-to-treat population;
N = number of subjects; PP = per protocol.

RESULTS

Subject Disposition and Demography:

A total of 126 subjects were selected and randomized in either Treatment Group A or Treatment Group B to participate in the study. However, 18 of those randomized subjects were considered Screening failures and, as such, did not receive any treatment related to the study. Demographic characteristics are presented in Table 3.

Table 3. Demographic Characteristics

Variable	Treatment Group A	Treatment Group B
Age (years), mean (SD), median	40.22(10.36), 41.06	42.63(10.66), 41.97
Sex		
Male, N (%)	43 (79.63)	43 (79.63)
Female, N (%)	11 (20.37)	11 (20.37)
Race		
White, N (%)	54 (100)	51 (94.44)
Other, N (%)	0	2 (3.70)

A = 50 mg twice in a week; B = 50 mg once in a week; N = number of subjects; SD = standard deviation.

Eleven (11) subjects discontinued from the study, 5 in Group A and 6 in Group B, after beginning the treatment. The reasons for these discontinuations are provided in Table 4.

Table 4. Reasons for Discontinuations From the Study

Treatment	Reason For Withdrawal	Number of Subjects	%
A	Protocol deviation	5	9.26
B	Other	1	1.85
	Protocol deviation	2	3.70
	AE	2	3.70
	Subject's decision	1	1.85

A = 50 mg twice in a week; AE = adverse event; B = 50 mg once in a week.

Efficacy Results: A total of 108 out of 126 subjects enrolled were randomized to Treatment Group A and Treatment Group B (54 subjects each). The treatment groups were comparable regarding baseline characteristics. Regarding disease factors both groups were not significantly different at Baseline with the exception of Human leukocyte antigen B27 (HLA-B27) molecule which was carried by 90.57% of Treatment Group A subjects compared to 74.07% of Treatment Group B subjects (p=0.04). Disease evaluations and measures were also comparable among groups. The burden of the disease assessed by SF-36 and EuroQol questionnaires also showed similar results at Baseline between Treatment Group A and Treatment Group B.

All subjects received at least 1 dose of any treatment. There were no statistically significant differences regarding extent of exposure between both arms of Treatment (mean administered injections by subject were 22.02±5.45 and 22.43±4.91 and mean duration of the treatment was 10.45 and 10.79 weeks for Treatment Group A and Treatment Group B, respectively).

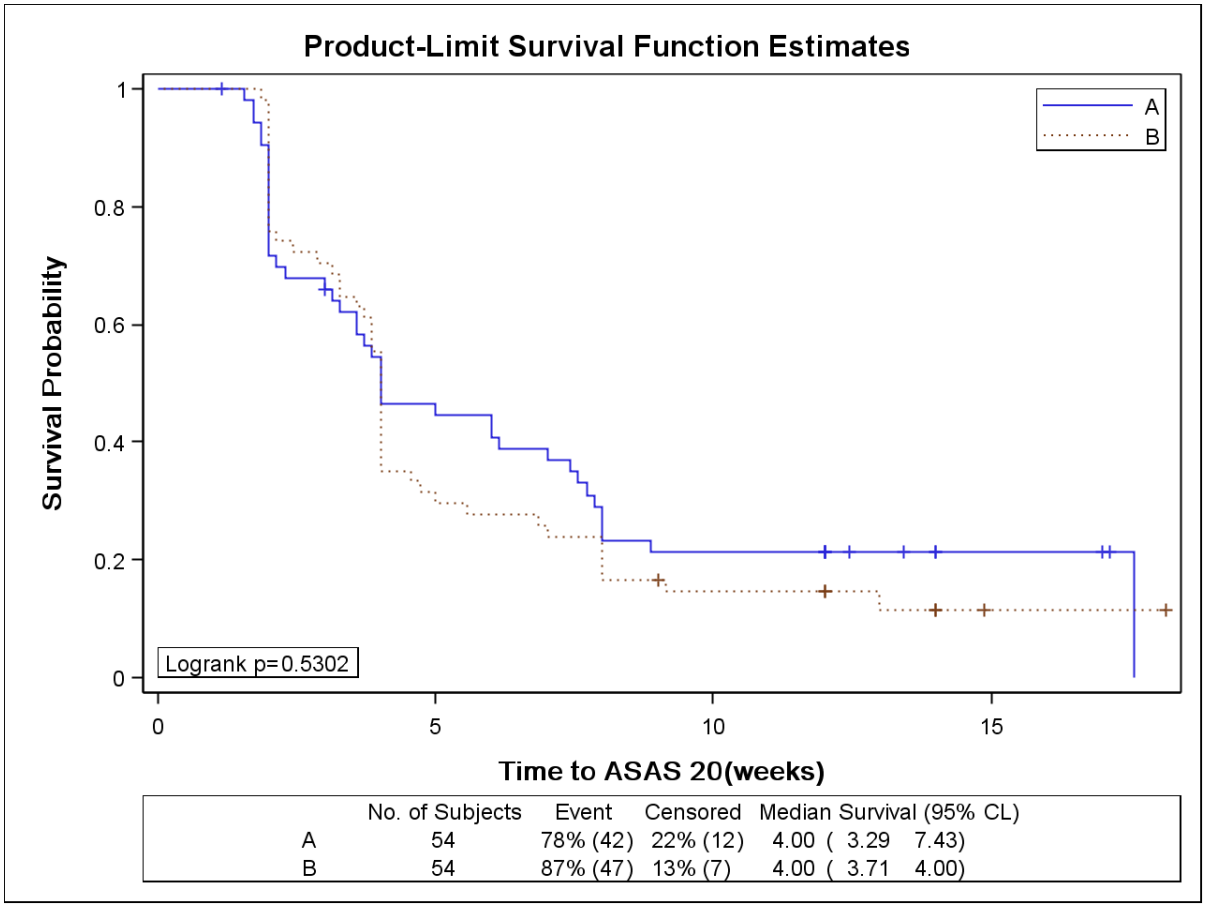
Primary Efficacy Endpoint Results: Table 5 represents the ASAS 20 rate of responders, the primary endpoint, of both the ITT and PP populations at Week 12 and last observation was evaluated. Figure 1 Shows time to ASAS 20 (Weeks) response.

Table 5. Proportion of Responders (ASAS 20) at Week 12 and Last Observation

Variable	Treatment A	Treatment B
ITT population		
ASAS 20 (Week 12); N (%)	34 (70.83)	37 (75.51)
ASAS 20 (last observation); N (%)	38 (70.37)	41 (75.93)
PP population		
ASAS 20 (Week 12); N (%)	32 (74.42)	32 (72.73)
ASAS 20 (last observation); N (%)	32 (74.42)	32 (72.73)

A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; ITT = intent-to-treat population; N = number of subjects; PP = per protocol.

Figure 1. Time to ASAS 20 (Weeks)



A = 50 mg twice in a week; ASAS 20 = assessment in ankylosing spondylitis B = 50 mg once in a week; CL = confidence limits.

Secondary Efficacy Endpoint Results: Table 6 shows ASAS 40 and (52.08% in Treatment Group A vs 51.02% in Treatment Group B); Table 7 shows ASAS 50 (45.83% in Treatment

Group A and 48.98% in Treatment Group B), Table 8 shows ASAS 70 (31.25% in Treatment Group A and 40.82% in Treatment Group B) and ASAS 5/6 (41.67% in Treatment Group A and 44.90% in Treatment Group B), more subjects achieved these indexes of response in Treatment Group B than in Treatment Group A, but as for the primary endpoint the differences did not reach statistical significance. By contrast, a measure of disease activity as BASDAI 50% showed a higher proportion of subjects reaching this index in Treatment Group A (66.67% and 62.96%, at Week 12 and last observation, respectively) than in Treatment Group B (55.10% and 53.70% at Week 12 and last observation, respectively), although it was not significant. In addition, a major therapeutic barrier as partial remission was achieved by nearly 30% of subjects in both groups.

ASAS 40, ASAS 50, ASAS 70 and ASAS 5/6: The ASAS 40 response represents (Figure 2) improvement of at least 40% and absolute improvement of at least 2 units (on a scale of 0-10) compared with baseline in at least 3 of the 4 domains of the ASAS 20 criteria, with absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0-100 scale) in the potential remaining domain.

Table 6. Proportion of Responders (ASAS 40) at Week 12 and Last Observation

Variable	Treatment Group A	Treatment Group B
ASAS 40 (Week 12); N (%)	25 (52.08)	25 (51.02)
ASAS 40 (last observation); N (%)	27 (50.00)	27 (50.00)

A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; N = number of subjects.

Table 7. Proportion of Responders (ASAS−50) at Week 12 and Last Observation

Variable	Treatment Group A	Treatment Group B
ASAS 50 (Week 12); N (%)	22 (45.83)	24 (48.98)
ASAS 50 (last observation); N (%)	24 (44.44)	25 (46.30)

A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; N = number of subjects.

Table 8. Proportion of Responders (ASAS−70) at Week 12 and Last Observation

Variable	Treatment Group A	Treatment Group B
ASAS 70 (Week 12); N (%)	15 (31.25)	20 (40.82)
ASAS 70 (last observation); N (%)	15 (27.78)	20 (37.04)

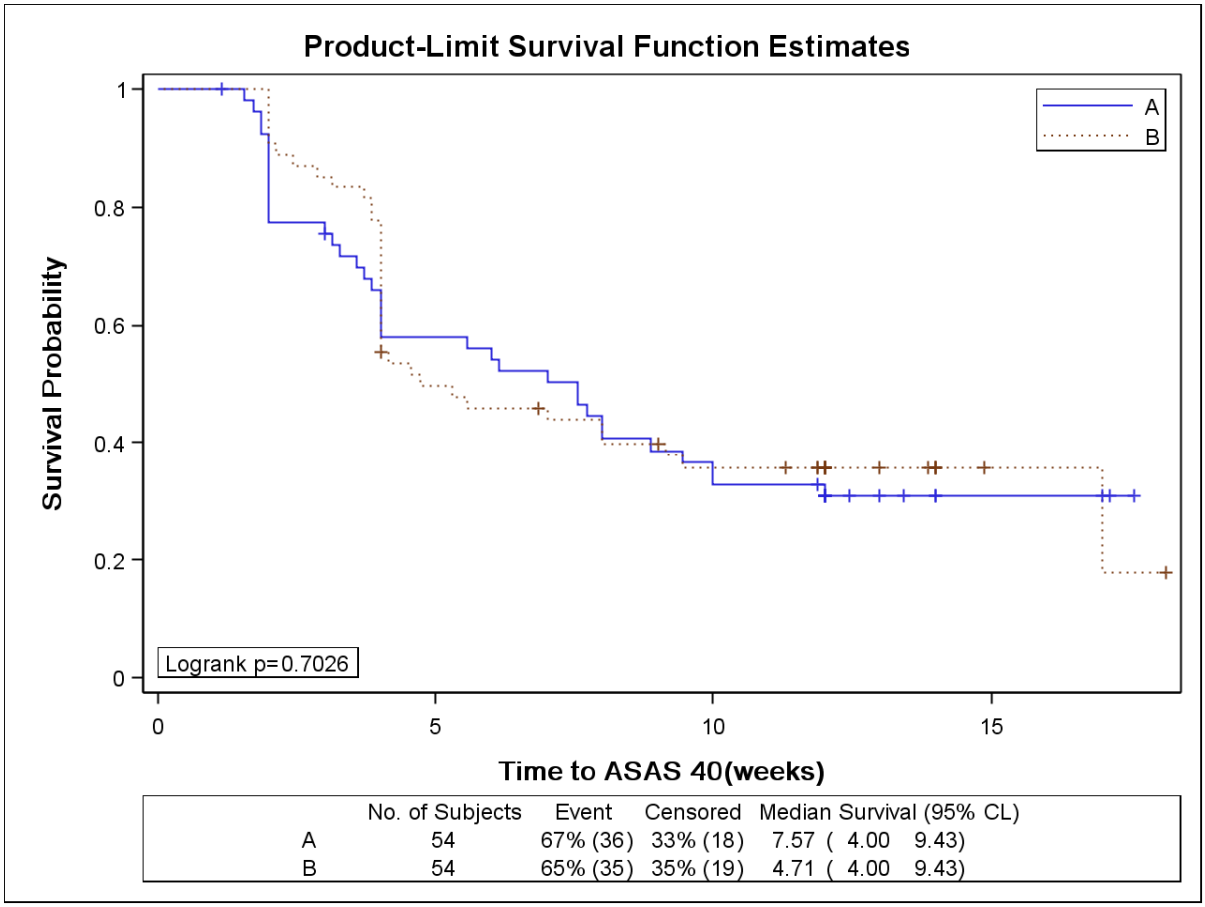
A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; N = number of subjects.

Table 9. Proportion of Responders (ASAS 5/6) at Week 12 and Last Observation

Variable	Treatment Group A	Treatment Group B
ASAS 5/6 (Week 12); N (%)	20 (41.67)	22 (44.90)
ASAS 5/6 (last observation); N (%)	21 (38.89)	26 (48.15)

A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; N = number of subjects.

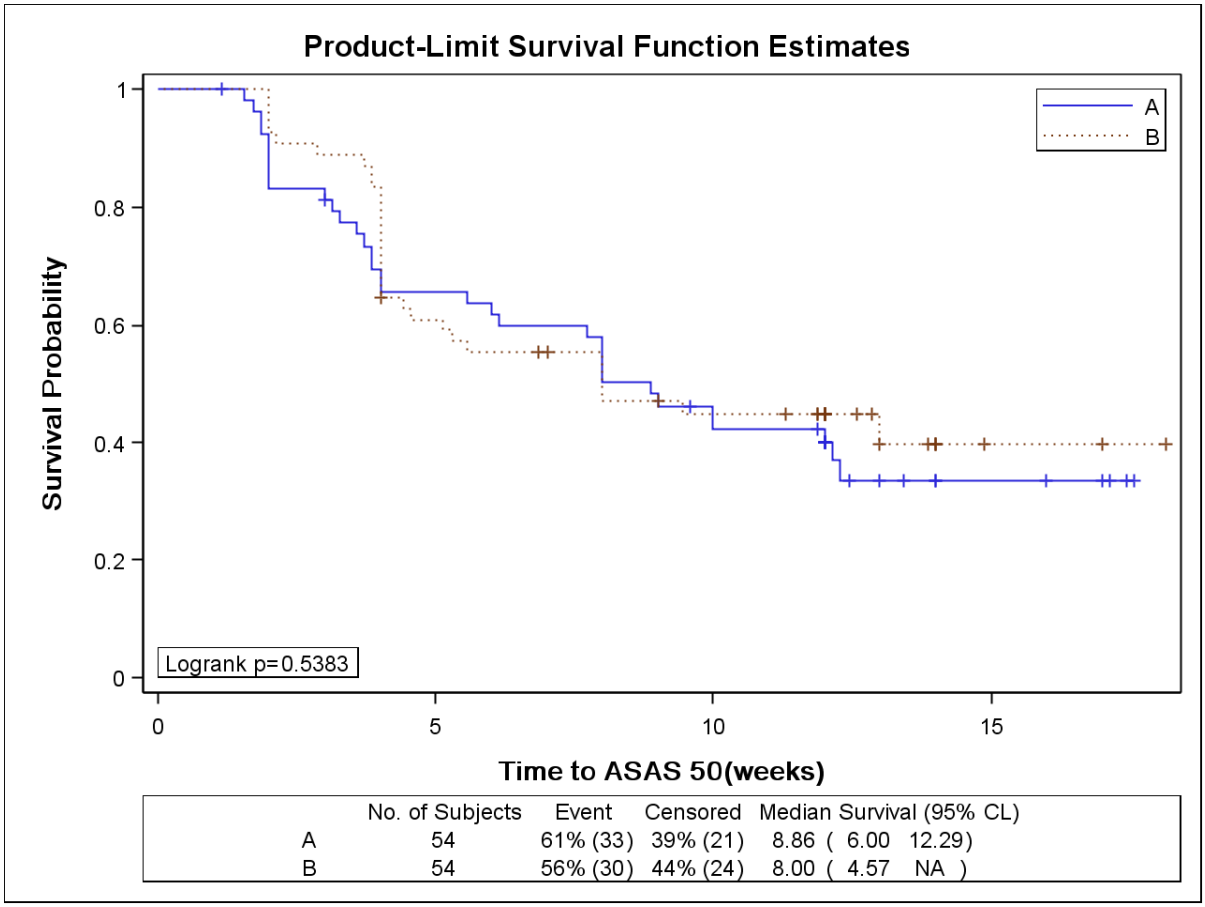
Figure 2. Time to ASAS 40 (Weeks)



A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; CL = confidence limits.

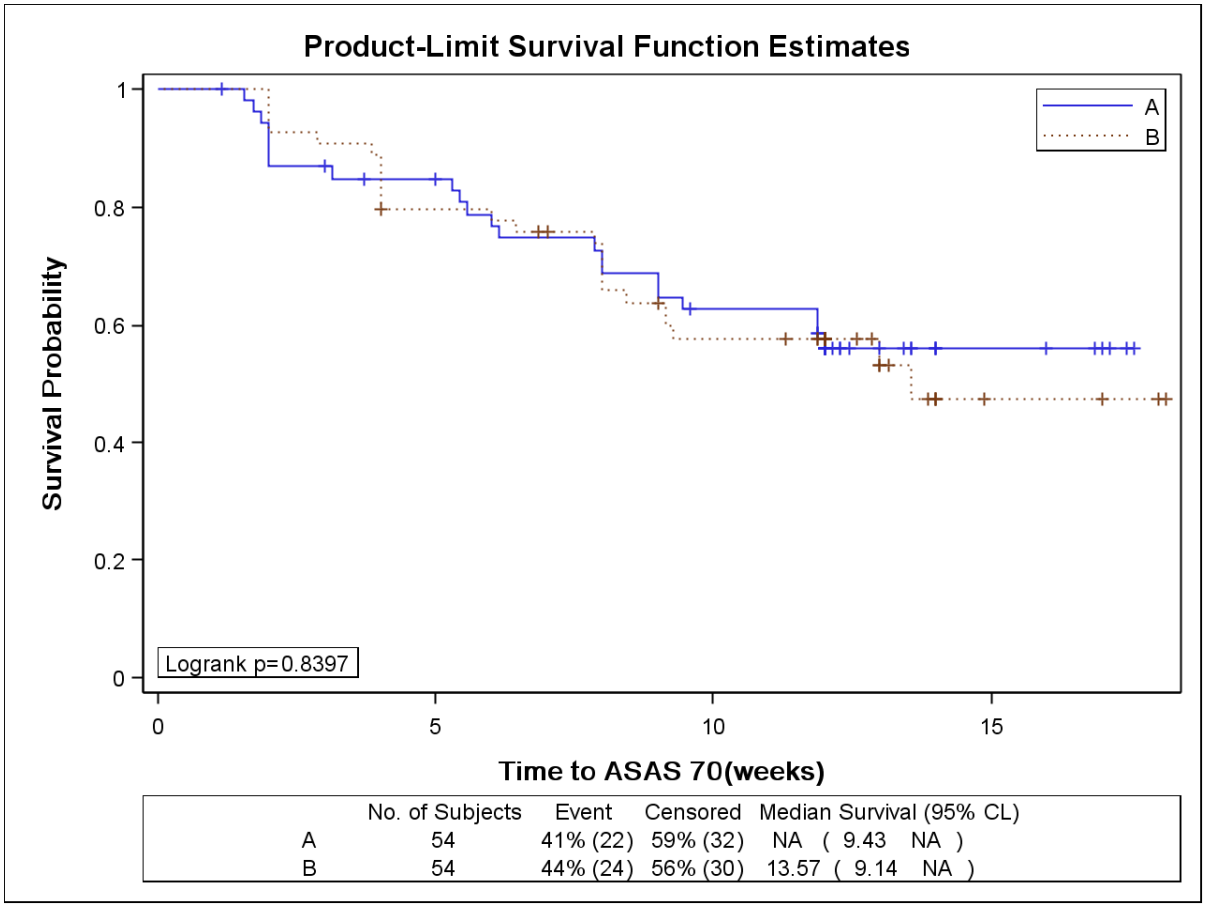
To achieve ASAS 50 (Figure 3) and ASAS 70 (Figure 4) responses is needed to improve at least 50% and 70%, respectively, in at least 3 of the 4 domains of the ASAS 20 criteria, with absence of deterioration (of at least 20% and absolute change of at least 10 units on a 0-100 scale) in the potential remaining domain.

Figure 3. Time to ASAS 50 (Weeks)



A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; CL = confidence limits.

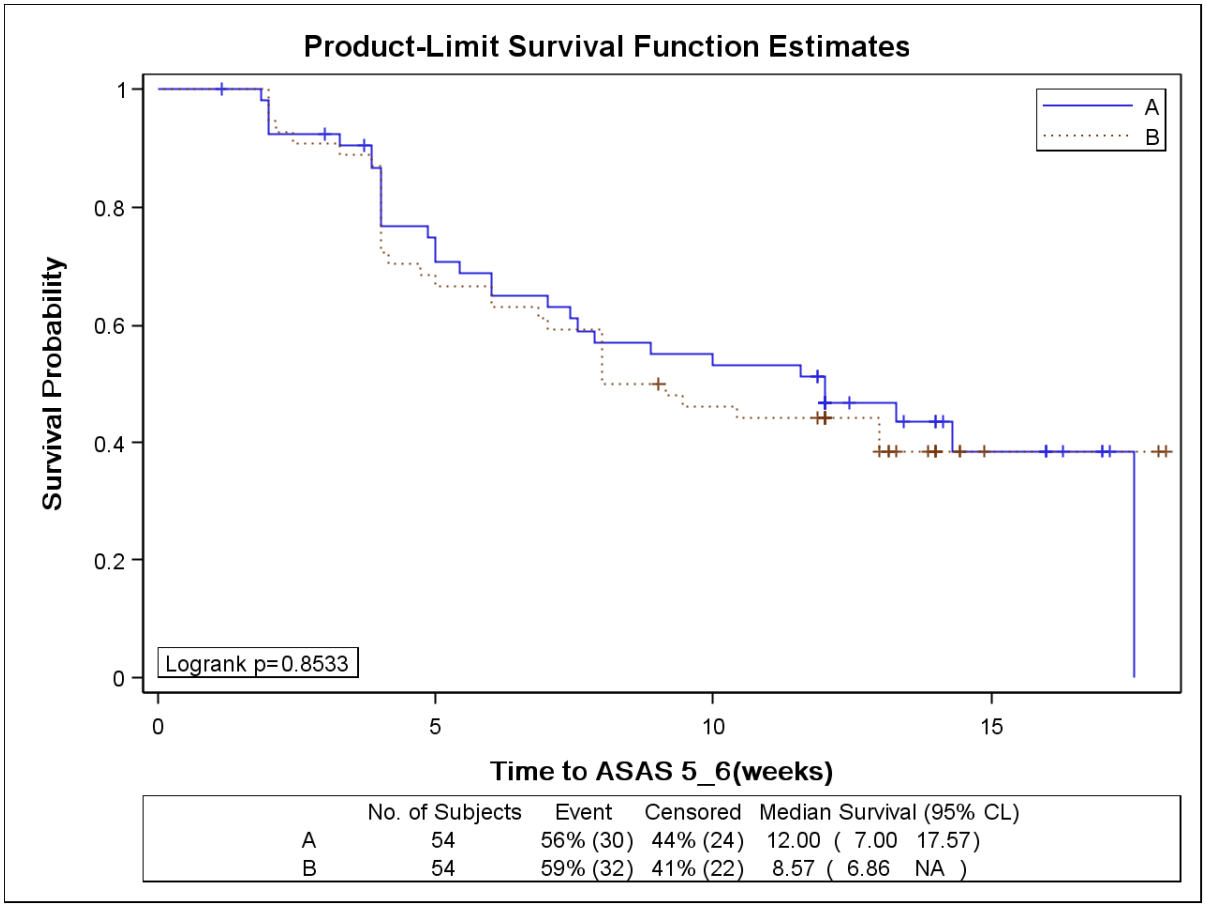
Figure 4. Time to ASAS 70 (Weeks)



A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; CL = confidence limits.

The ASAS 5/6 (Figure 5) requires an improvement of at least 20% in 5 of 6 domains: the 4 domains of the ASAS 20 in addition to CRP concentration and spinal mobility (BASMI).

Figure 5. Time to ASAS 5/6 (Weeks)



A = 50 mg twice in a week; ASAS = assessment in ankylosing spondylitis; B = 50 mg once in a week; CL = confidence limits.

Of the subjects receiving Treatment Group A, 52.08% (25 of 48) achieved and ASAS 40 response at Week 12 compared with 51.02% (25 of 49) of those subjects receiving Treatment Group B. In both groups the proportion of subjects who achieved ASAS 50 was quite similar to ASAS 40 (45.83% in Treatment Group A and 48.98% in Treatment Group B). None of these differences between Treatment Group A and Treatment Group B were statistically significant (ASAS 40: p=0.92; ASAS 50: p=0.76). With respect to ASAS 70, 15 subjects (31.25%) in Treatment Group A and 20 (40.82%) in Treatment Group B achieved this level of response at Week 12. This difference was not statistically significant (p=0.33). The ASAS 5/6, 20 subjects (41.67%) in Treatment Group A and 22 (44.90%) in Treatment Group B achieved the ASAS 5/6 response at Week 12 (p=0.75).

The results presented above did not differ significantly if subjects who discontinued before Week 12 were also included.

Time to Response (ASAS 40, 50, 70 and 5/6): Survival analysis using the Kaplan-Meyer method were performed for the ITT population. The Log-rank test was used to detect if there was significant effect of the treatment in the time to response.

Regarding ASAS 40 no statistically significant differences due to the treatment (p=0.7026) were observed. The median time was reached at 7.57 weeks with a confidence interval (CI) 95% (4.00, 9.43) weeks for Treatment Group A and 4.71 weeks with a CI 95% (4.00, 9.43) weeks for Treatment Group B.

The rates of response along endpoints for both groups (67% for Treatment Group A vs 65% for Treatment Group B) were very different from the rates of response at week 12 (52.08% vs 51.02%), and were very similar in both Treatment Group A (67%) and Treatment Group B (65%).

Partial Remission: Table 10 shows partial remission at Week 12, 14 subjects in Treatment Group A (29.17%) and 13 in Treatment Group B (26.53%) had this status (p=0.77). After including the subjects withdrawn before Week 12 (last observation) the proportion of subjects in whom the disease had partially remitted remained almost identical (27.78% vs 24.07%; p=0.66).

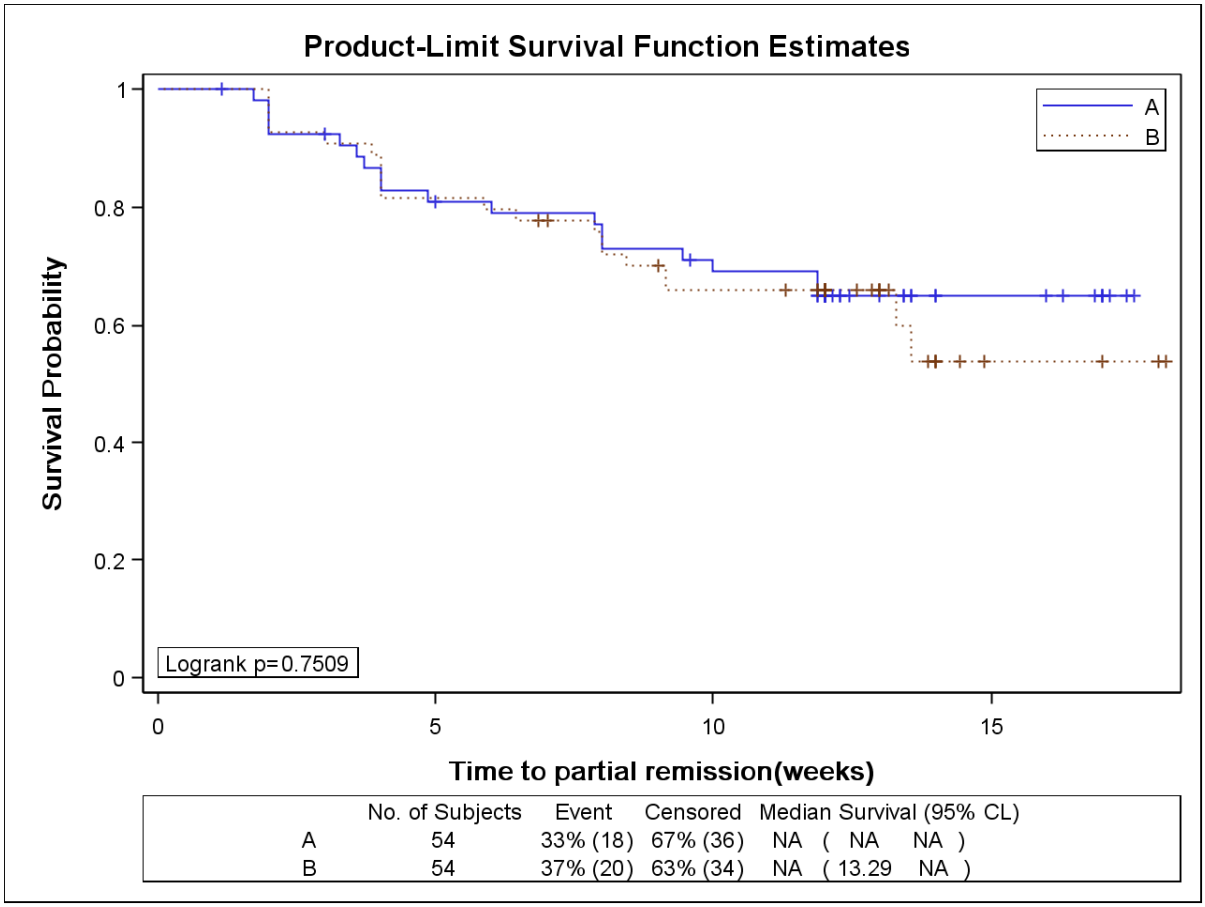
Table 10. Partial Remission at Week 12 and Last Observation

Partial Remission	Treatment Group A	Treatment Group B
Week 12; N (%)	14 (29.17)	13 (26.53)
Last observation; N (%)	15 (27.78)	13 (24.07)

A = 50 mg twice in a week; B = 50 mg once in a week; N = number of subjects.

With regards to 'Time to response (ASAS 5/6) endpoints', a survival analysis using the Kaplan Meyer method was performed for the ITT population. The Log-rank test was used to detect if there was significant effect of the treatment in the time to response and no statistically significant differences due to the treatment (p=0.7509) were observed. The median time was not reached in any group. The rates of response along endpoints for both groups (33% for Treatment Group A vs 37% for Treatment Group B) were slightly different from the rates of response at Week 12 (29.17% vs 26.53%), and were very similar in both Treatment Group A (33%) and Treatment Group B (37%).Figure 6 shows partial remission at Week 12 and last observation.

Figure 6. Time to Partial Remission (Weeks)



A = 50 mg twice in a week; B = 50 mg once in a week; CL = confidence limits; NA = not available.

Changes From Baseline Visit and Per Visit in Nocturnal and Overall Spine Pain: Both nocturnal back pain (Table 11, Table 12) and total back pain (Table 13, Table 14) were assessed by subjects, in addition to baseline, at Weeks 1, 2, 3, 4, 8 and 12. The results of all these assessments were compared with the data from Baseline. Total back pain assessment presented mean values of 6.74 and 6.30 for Treatment Group A and Treatment Group B respectively. Early, at Week 1 the total back pain assessment by subjects experienced an important mean reduction in both groups of treatment (-2.61 in Treatment Group A vs -2.16 in Treatment Group B). These reductions were statistically significant ($p<0.0001$; CI 95% of Treatment Group A [-3.47, -1.75]; CI 95% of Treatment Group B {-2.93, -1.38}).

Table 11. Nocturnal Back Pain-Treatment Group A (Changes Per Visit From Baseline)

Nocturnal Back Pain(A)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	49	51	48	50	49	48	54
Mean	-2.92	-3.20	-3.00	-3.18	-3.85	-3.96	-3.84
SD	3.13	2.95	3.36	3.02	3.10	3.15	3.05
Median	-2.70	-3.60	-3.15	-3.15	-3.60	-4.60	-4.55
Range	5.10	4.50	5.60	5.20	4.10	4.55	4.50
Minimum	-9.50	-9.00	-9.80	-9.60	-9.20	-10.0	-10.0
Maximum	3.10	2.10	4.60	2.00	2.70	1.40	1.40
Lower 95% CI	-3.82	-4.03	-3.97	-4.03	-4.74	-4.87	-4.67
Upper 95% CI	-2.02	-2.37	-2.02	-2.32	-2.96	-3.05	-3.00
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 12. Nocturnal Back Pain-Treatment Group B (Changes Per Visit From Baseline)

Nocturnal Back Pain(B)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	53	53	52	51	49	49	54
Mean	-2.57	-2.82	-3.12	-3.65	-4.08	-4.15	-4.07
SD	2.72	2.58	2.96	2.64	2.69	2.76	2.72
Median	-2.40	-3.10	-3.15	-3.40	-4.20	-4.40	-4.20
Range	3.70	3.70	4.65	4.50	4.50	4.20	4.20
Minimum	-8.60	-7.50	-9.00	-9.20	-9.80	-9.90	-9.90
Maximum	4.90	6.30	4.90	2.00	1.00	2.50	2.50
Lower 95% CI	-3.32	-3.53	-3.94	-4.39	-4.85	-4.95	-4.81
Upper 95% CI	-1.82	-2.11	-2.29	-2.90	-3.30	-3.36	-3.32
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

The fall continued for both groups in the following weeks, being statistically significant compared with baseline, achieving a maximum mean decrease at Week 12 (-3.89 vs -3.53; p<0.0001; CI 95%: -4.75, -3.02 and -4.35, -2.72 for Treatment Groups A and B respectively). Regarding the last observation, the mean reduction for Treatment Group A was -3.84 while for Treatment Group B was -3.47. Again, these differences were statistically significant with respect to baseline (p<0.0001; CI 95% of Treatment Group A [-4.63, -3.06]; CI 95% of Treatment Group B {-4.23, -2.71}).

Table 13. Total Back Pain-Treatment Group A (Changes Per Visit From Baseline)

Total Back Pain(A)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	49	51	48	50	49	48	54
Mean	-2.61	-2.93	-2.92	-3.05	-3.54	-3.89	-3.84
SD	2.99	2.85	2.99	2.98	2.93	2.99	2.87
Median	-2.20	-3.20	-2.95	-3.15	-4.20	-4.30	-3.75
Range	4.40	4.80	5.10	4.40	4.10	4.90	4.40
Minimum	-8.10	-8.30	-8.30	-8.60	-8.90	-10.0	-10.0
Maximum	3.40	2.70	2.40	2.80	1.50	2.20	2.20
Lower 95% CI	-3.47	-3.73	-3.79	-3.90	-4.38	-4.75	-4.63
Upper 95% CI	-1.75	-2.13	-2.05	-2.21	-2.70	-3.02	-3.06
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 14. Total Back Pain-Treatment Group B (Changes Per Visit From Baseline)

Total Back Pain(B)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	53	53	52	51	49	49	54
Mean	-2.16	-2.39	-2.95	-3.34	-3.73	-3.53	-3.47
SD	2.81	2.53	2.67	2.44	2.75	2.85	2.78
Median	-1.70	-2.20	-3.05	-3.40	-4.00	-3.90	-3.85
Range	3.40	3.30	2.90	3.50	3.30	3.70	4.00
Minimum	-7.90	-8.50	-9.00	-8.80	-9.50	-9.60	-9.60
Maximum	7.10	5.50	2.40	0.90	2.10	3.00	3.00
Lower 95% CI	-2.93	-3.08	-3.69	-4.03	-4.52	-4.35	-4.23
Upper 95% CI	-1.38	-1.69	-2.21	-2.65	-2.94	-2.72	-2.71
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Nocturnal back pain showed a very similar tendency to total back pain, improving from Week 1 and reaching a minimum value (maximum difference with respect to baseline) at Week 12 and last observation. All differences vs baseline were statistically significant; however, when compared all these differences between both groups of treatment, for either total or nocturnal back pain, there were not statistically significant differences.

Change From Baseline Visit and Per Visit in Subject Global Assessment, and Physician Global Assessment: For subject assessment mean values (Table 15, Table 16), at Baseline were 6.75 for Treatment Group A and 6.97 for Treatment Group B, reflected improvement at Week 1 for both groups (-2.70 vs -2.68). Again, the maximum improvement was achieved at Week 12 and last observation in Treatment Group A (-3.67 and -3.60 respectively). However, in Treatment Group B the maximum improvement was earlier, at Week 8 (-4.26).

Nevertheless, mean changes at Week 12 and last observation were rather similar to that referred at Week 8 (-4.17 and -4.00 respectively).

Table 15. Subject Global Assessment-Treatment Group A (Changes Per Visit From Baseline)

Subject Global Assessment (A)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	49	51	48	50	49	48	54
Mean	-2.70	-2.82	-2.81	-3.17	-3.31	-3.67	-3.60
SD	2.75	2.61	2.87	2.67	2.81	3.13	3.04
Median	-2.80	-2.60	-3.10	-3.40	-3.20	-3.75	-3.90
Range	4.00	4.00	4.45	4.20	3.80	4.25	4.10
Minimum	-8.30	-8.50	-8.50	-8.50	-9.00	-10.0	-10.0
Maximum	3.00	3.10	2.30	3.90	3.20	6.10	6.10
Lower 95% CI	-3.49	-3.56	-3.64	-3.93	-4.12	-4.58	-4.43
Upper 95% CI	-1.91	-2.09	-1.98	-2.41	-2.50	-2.76	-2.77
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 16. Subject Global Assessment-Treatment Group B (Changes Per Visit From Baseline)

Subject Global Assessment (B)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	53	53	52	51	49	49	54
Mean	-2.68	-3.23	-3.56	-3.93	-4.26	-4.17	-4.00
SD	2.73	2.50	2.48	2.52	2.79	2.69	2.79
Median	-2.60	-2.90	-3.50	-3.60	-4.40	-4.70	-4.10
Range	3.50	4.10	3.35	3.80	3.70	4.20	4.30
Minimum	-8.30	-8.50	-9.30	-8.90	-9.50	-9.40	-9.40
Maximum	3.20	2.60	0.70	1.50	1.80	0.60	3.20
Lower 95% CI	-3.44	-3.91	-4.25	-4.64	-5.06	-4.94	-4.76
Upper 95% CI	-1.93	-2.54	-2.87	-3.22	-3.46	-3.40	-3.24
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

In comparison to Baseline (mean values: 6.01 vs. 5.82) global assessment by Physician (Table 17, Table 18) improved at Week 2 for both groups of subjects (-2.81, 46.8% vs -2.84, 48.8%). These improvement continued over the following weeks reaching a mean maximal improvement at Week 12 (-4.15, 69.1% vs -4.12, 70.8%) and last observation (-4.17, 69.4% vs -3.99, 68.6%).

Although the changes at every week were statistically significant compared to baseline ($p<0.0001$), the comparison between Treatment Groups A and B of treatment did not reach significant values.

All changes were significantly different from Baseline ($p<0.0001$), but not the comparison between both treatment arms.

Table 17. Physician Global Assessment-Treatment Group A (Changes Per Visit From Baseline)

Physician Global Assessment (A)	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54
Mean	-2.81	-3.15	-3.63	-4.15	-4.17
SD	1.68	1.91	2.06	1.77	1.71
Median	-2.90	-3.00	-3.80	-4.20	-4.30
Range	2.60	2.70	2.40	2.15	2.00
Minimum	-6.10	-6.60	-8.80	-8.80	-8.80
Maximum	1.00	1.20	2.00	0.10	0.10
Lower 95% CI	-3.28	-3.69	-4.22	-4.66	-4.63
Upper 95% CI	-2.34	-2.61	-3.04	-3.63	-3.70
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 18. Physician Global Assessment-Treatment Group B (Changes Per Visit From Baseline)

Physician Global Assessment (B)	Week 2	Week 4	Week 8	Week 12	Last Observation
N	53	51	49	49	54
Mean	-2.84	-3.35	-3.67	-4.12	-3.99
SD	1.48	1.41	1.51	1.39	1.43
Median	-2.90	-3.40	-3.90	-4.20	-4.05
Range	2.00	1.90	2.30	2.30	2.10
Minimum	-6.10	-6.20	-6.40	-6.60	-6.60
Maximum	0.20	0.00	-0.50	-0.80	-0.40
Lower 95% CI	-3.25	-3.74	-4.10	-4.51	-4.38
Upper 95% CI	-2.43	-2.95	-3.23	-3.72	-3.60
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

BASFI (Changes Per Visit From Baseline): As for previously analyzed secondary endpoints, a clear improvement regarding mean BASFI changes from Baseline was observed at Week 2 for any Treatment Group (-1.80 in A and -1.61 in B).

BASFI index continued improving until Week 12 and last observation. However, for Treatment Group B the maximum change was at Week 8 (absolute change:-2.48, percentual change: 43.8%), almost identical to Week 12 (-2.45, 43.3%). All mean changes for both groups were statistically significant with regard to baseline (p<0.0001). The differences observed were not significant when compared those mean changes between Treatment Group A and Treatment Group B.

A summary of BASFI data shown in Table 19 and Table 20.

Table 19. BASFI Score-Treatment Group A (Changes Per Visit From Baseline)

BASAFI Score (A)	Week 2	Week 4	Week 8	Week 12	Last Observation
N	50	50	49	48	54
Mean	-1.80	-1.91	-2.32	-2.61	-2.44
SD	2.43	2.55	2.39	2.64	2.63
Median	-1.25	-1.55	-1.97	-2.48	-2.37
Range	3.31	3.97	3.46	3.68	3.30
Minimum	-6.83	-6.87	-7.28	-8.24	-8.24
Maximum	2.88	3.21	3.06	3.24	3.24
Lower 95% CI	-2.49	-2.63	-3.01	-3.38	-3.16
Upper 95% CI	-1.11	-1.18	-1.64	-1.84	-1.72
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 20. BASFI Score-Treatment Group B (Changes Per Visit From Baseline)

BASFI Score (B)	Week 2	Week 4	Week 8	Week 12	Last Observation
N	53	51	49	49	54
Mean	-1.61	-2.22	-2.48	-2.45	-2.36
SD	1.83	1.82	2.10	2.12	2.08
Median	-1.73	-2.30	-2.30	-2.14	-1.97
Range	2.35	2.17	2.82	3.78	3.53
Minimum	-5.82	-7.44	-8.27	-7.09	-7.09
Maximum	4.07	1.45	1.07	1.91	1.91
Lower 95% CI	-2.12	-2.73	-3.09	-3.06	-2.93
Upper 95% CI	-1.11	-1.71	-1.88	-1.84	-1.79
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; BASFI = Bath Ankylosing Spondylitis Functional Index; CI = confidence interval; N = number of subjects; SD = standard deviation.

BASDAI (Changes Per Visit From Baseline): At Week 1 an improvement was detectable as the mean score was significantly lower in both groups with respect to baseline (-2.22 vs -2.38; p<0.0001). The change increased almost parallel in both groups during the following weeks. In Group A the maximum improvement was reached at Week 8 and Week 12 (-3.42, 56.1% vs -3.67, 60.2%). However, in Group B the mean greater improvement was at Week 8 (-3.70; 57.1%), although rather similar to the amelioration at both Week 12 and last observation (-3.59, 55.4% and -3.58, 55.2%). No significant differences were detected when compared both groups of treatment.

A summary of BASDAI data shown in Table 21 and Table 22.

Table 21. BASDAI-Treatment Group A (Changes Per Visit From Baseline)

BASDAI (A)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	49	51	48	50	49	48	54
Mean	-2.22	-2.63	-2.67	-2.98	-3.42	-3.67	-3.35
SD	2.04	2.15	2.35	2.24	2.13	2.18	2.32
Median	-2.47	-3.25	-2.58	-3.13	-3.67	-4.12	-3.85
Range	2.88	3.13	3.27	2.88	2.55	2.20	3.32
Minimum	-6.68	-7.80	-7.77	-7.98	-7.38	-7.47	-7.47
Maximum	1.87	1.77	2.12	1.80	1.38	0.83	2.30
Lower 95% CI	-2.81	-3.23	-3.35	-3.62	-4.03	-4.31	-3.98
Upper 95% CI	-1.64	-2.02	-1.98	-2.34	-2.81	-3.04	-2.71
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index;
CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 22. BASDAI-Treatment Group B (Changes Per Visit From Baseline)

BASDAI (B)	Week 1	Week 2	Week 3	Week 4	Week 8	Week 12	Last Observation
N	53	53	52	51	49	49	54
Mean	-2.38	-2.77	-3.25	-3.52	-3.70	-3.59	-3.58
SD	1.98	2.25	2.00	2.09	2.39	2.46	2.43
Median	-2.27	-2.65	-3.03	-3.50	-3.77	-3.90	-3.65
Range	2.23	2.93	2.12	2.00	2.25	2.90	2.90
Minimum	-7.48	-7.48	-8.03	-7.78	-8.45	-8.68	-8.68
Maximum	0.97	1.47	1.10	1.12	1.30	1.55	1.55
Lower 95% CI	-2.93	-3.39	-3.81	-4.10	-4.39	-4.30	-4.24
Upper 95% CI	-1.83	-2.15	-2.69	-2.93	-3.02	-2.88	-2.91
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

B = 50 mg once in a week; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index;
CI = confidence interval; N = number of subjects; SD = standard deviation.

The proportion of subjects who achieved at least a 50% increase in the BASDAI score (Table 23) at every visit was also analyzed.

For both groups such improvement was achieved at Week 1 by 38.00% of subjects in Treatment Group A and 30.19% in Treatment Group B. In the following visits the proportion of subjects reaching BASDAI 50% increased in general and always was >40%. However, in Treatment Group A the proportion decreased at Week 3 (43.75%) with respect to Week 2 (52.94%) and in Treatment Group B at Week 12 (55.10%) with respect to Weeks 4 (58.82%) and 8 (59.18%). At Week 12 and last observation the frequency of subjects with BASDAI 50% in Treatment Group A was 66.67% and 62.96%, while in Treatment Group B was 55.10% and 53.70%, respectively. There were not significant differences at any time point between both arms of treatment.

Table 23. BASDAI 50% Per Visit

50% Improvement on BASDAI	Week 1 N (%)	Week 2 N (%)	Week 3 N (%)	Week 4 N (%)	Week 8 N (%)	Week 12 N (%)	Last Observation N (%)
BASDAI 50% (A)	19 (38.00)	27 (52.94)	21 (43.75)	27 (54.00)	32 (65.31)	32 (66.67)	34 (62.96)
BASDAI 50% (B)	16 (30.19)	23 (43.40)	25 (48.08)	30 (58.82)	29 (59.18)	27 (55.10)	29 (53.70)

A = 50 mg twice in a week; B = 50 mg once in a week;
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index;
N = number of subjects.

BASMI Score: In Treatment Groups A and B, BASMI score showed an improvement at Week 2 and this amelioration continued in the following weeks reaching maximum changes at Week 12 and last observation. Nevertheless, the improvement was greater in Treatment Group B subjects than in Treatment Group A subjects.

At Week 2 mean change in Treatment Group A was -0.23 (6.8%) and being non significant. By contrast, in Treatment Group B at the same time point the mean change was -0.44 (14.2%) and statistically significant (p=0.0054). After Week 2, the mean changes were statistically significant for both Groups. At Week 12, the mean changes were -0.46 (13.5%) and -0.80 (25.8%) for Treatment Groups A and B, respectively. Last observation mean changes were very similar to Week 12 (-0.45 and -0.88). In spite of these differences between both treatment groups with respect to baseline values, the comparison of the Groups was not statistically significant at any time point. In addition, an analysis of the changes in the 5 variables comprising the BASMI score (Table 24) was undergone. The following results were observed:

Table 24. BASMI Score (Changes Per Visit From Baseline)

BASMI Score	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	48	45	47	46	51	48	47	45	45	50
Mean	-0.23	-0.31	-0.32	-0.46	-0.45	-0.44	-0.60	-0.76	-0.80	-0.88
SD	0.86	1.00	1.04	0.98	0.99	1.09	0.95	1.05	1.27	1.30
Median	0.00	0.00	0.00	-1.00	-1.00	0.00	0.00	-1.00	-1.00	-1.00
Range	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	2.00	2.00
Minimum	-2.00	-2.00	-2.00	-3.00	-3.00	-4.00	-3.00	-3.00	-4.00	-4.00
Maximum	2.00	3.00	2.00	3.00	3.00	2.00	1.00	2.00	2.00	2.00
Lower 95% CI	-0.48	-0.61	-0.63	-0.75	-0.73	-0.75	-0.87	-1.07	-1.18	-1.25
Upper 95% CI	0.02	-0.01	-0.01	-0.16	-0.17	-0.12	-0.32	-0.44	-0.42	-0.51
Wilcoxon paired-test(p-value)	0.0868	0.0258	0.0354	0.0009	0.0007	0.0054	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; N = number of subjects; SD = standard deviation.

Cervical Rotation (Changes Per Visit From Baseline): Cervical rotation mean values (Table 25) at Baseline in Treatment Groups A and B were 60.15 and 60.69 degrees, respectively. Since Week 2 an improvement of 3.75 degrees (6.2%) was noticed in Treatment Group A, increasing in the following weeks and achieving maximum mean changes of 10.26 degrees (17.1%) at Week 12 and 10.52 (17.5%) at last observation. A similar tendency was observed in Treatment Group B, in which the improvement at Week 2 was 4.29 degrees (7.1%) and the maximum changes were at Week 12 (10.24 degrees, 16.9%) and last observation (10.81 degrees, 17.8%). However in Treatment Group B mean change at Week 4 (9.30 degrees) was higher than at Week 8 (8.35 degrees). All changes, less Week 2 difference in Treatment Group B, were statistically significant. The comparison between both groups was not significant.

Intermalleolar Distance (Changes Per Visit From Baseline): Intermalleolar distance (Table 26) improved in both groups since Week 2. However, the behaviour was quite different between them. In Treatment Group B the mean change at Week 2 was already significant (4.07, 4.3%, p=0.0043) while in Treatment Group A the mean improvement at the same time point was 2.10 cm (2.2%) and it was not significant. In addition, in Treatment Group A the difference showed increases and decreases until Week 12 and last observation in which intermalleolar distance reached a maximum improvement of 6.00 cm (6.4%) and 5.71 cm (6.1%). In Treatment Group B changes at Week 12 and last observation were 5.30 cm (5.6%) and 5.55 cm (5.9%) respectively, but the maximum improvement was at Week 8 with 6.45 cm (6.8%). Overall, all changes were significant in Treatment Group B, but not in Treatment Group A at Weeks 2 and 8. The comparison between both groups was not significant.

Modified Schober's Test (Changes Per Visit From Baseline): Mean values (Table 27) at baseline for Schober's test were 18.84 cm and 18.96 cm for Treatment Groups A and B, respectively. Mean improvements were detected in both Groups at Week 2, 0.21 cm in Treatment Group A and 0.38 cm in Treatment Group B. Maximum improvement was achieved at Week 12 and last observation in which the changes were for Treatment Group A 0.59 cm and 0.63 cm and for Treatment Group B there were 0.64 cm and 0.53 cm. All changes were statistically significant except the differences at Week 2 and 4 in Treatment Group A. The comparison between both groups was not statistically significant.

Lateral Flexion (Changes Per Visit From Baseline): Lateral flexion (Table 28) showed an early but non significant improvement, at Week 2, of 0.48 cm (4.3%) in Treatment Group B. In the following weeks the mean changes increased reaching a maximum mean improvement at Week 8 of 1.72 cm (15.6%; p<0.0001). Mean changes at Week 12 and last observation were 1.48 cm (13.4%) and 1.46 cm (13.2%), respectively. After Week 2, all changes were statistically significant in Treatment Group B.

In Treatment Group A mean lateral flexion worsened slightly at Week 2 (-0.16 cm). In the following weeks lateral flexion improved, but the maximum mean change of 0.94 cm (9.2%) was at Week 8 compared to increases of 0.28 cm (2.7%) at Week 12 and 0.49 cm (4.8%) at last observation. All changes were non significant. The comparison between both arms of treatment was not statistically significant.

Table 25. Cervical Rotation (°) [Changes Per Visit From Baseline]

Cervical Rotation	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	52	50	47	48	53
Mean	3.75	6.09	7.46	10.26	10.52	4.29	9.30	8.35	10.24	10.81
SD	12.20	13.36	14.99	17.22	16.81	13.58	16.39	11.86	15.07	15.19
Median	3.75	4.38	7.50	10.00	10.00	0.38	3.75	5.00	6.25	7.50
Range	8.75	12.50	16.00	19.00	20.00	10.38	16.00	12.50	15.50	15.00
Minimum	-30.0	-43.0	-40.0	-37.5	-37.5	-20.0	-16.3	-10.0	-25.5	-25.5
Maximum	33.75	40.00	35.00	59.50	59.50	66.00	70.25	40.00	65.50	65.50
Lower 95% CI	0.32	2.29	3.16	5.26	5.93	0.51	4.64	4.87	5.87	6.62
Upper 95% CI	7.18	9.88	11.77	15.26	15.11	8.07	13.95	11.83	14.62	14.99
Wilcoxon paired-test(p-value)	0.0198	<0.0001	0.0003	<0.0001	<0.0001	0.0658	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 26. Intermalleolar Distance (Cm) [Changes Per Visit From Baseline]

Intermalleolar Distance (cm)	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	49	49	48	54	51	50	48	47	52
Mean	2.10	3.99	2.53	6.00	5.71	4.07	4.24	6.45	5.30	5.55
SD	10.19	9.38	11.68	14.46	14.19	9.63	8.37	7.09	9.60	9.32
Median	0.25	2.50	3.00	6.00	6.00	1.00	2.25	5.25	3.50	3.75
Range	7.50	9.25	10.00	13.97	13.45	12.00	8.50	9.75	9.50	10.17
Minimum	-22.0	-19.5	-29.0	-50.5	-50.5	-25.0	-14.5	-5.00	-19.0	-19.0
Maximum	33.50	30.00	37.75	42.75	42.75	33.00	32.00	24.50	29.50	29.50
Lower 95% CI	-0.77	1.30	-0.82	1.80	1.84	1.36	1.86	4.39	2.48	2.95
Upper 95% CI	4.96	6.69	5.89	10.20	9.58	6.78	6.62	8.51	8.12	8.14
Wilcoxon paired-test(p-value)	0.1318	0.0026	0.0578	0.0003	0.0002	0.0043	0.0002	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 27. Modified Schober's Test (Changes Per Visit From Baseline)

Modified Schober's Test	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	0.21	0.18	0.36	0.59	0.63	0.38	0.37	0.49	0.64	0.53
SD	0.95	1.37	1.15	1.14	1.20	1.48	1.18	1.53	1.60	1.61
Median	0.15	0.00	0.25	0.25	0.38	0.05	0.25	0.75	0.35	0.30
Range	0.85	1.25	1.00	1.53	1.50	1.25	1.05	1.70	1.30	1.25
Minimum	-3.00	-4.15	-2.65	-2.25	-2.25	-4.25	-3.00	-4.25	-4.10	-4.10
Maximum	2.25	3.25	3.00	3.00	3.25	4.55	4.55	4.60	6.40	6.40
Lower 95% CI	-0.06	-0.21	0.03	0.26	0.31	-0.03	0.04	0.05	0.18	0.09
Upper 95% CI	0.47	0.57	0.69	0.92	0.96	0.79	0.71	0.93	1.10	0.97
Wilcoxon paired-test(p-value)	0.1324	0.1795	0.0082	0.0006	0.0002	0.0462	0.0139	0.0099	0.0009	0.0052

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 28. Lateral Flexion (Cm) [Changes Per Visit From Baseline]

Lateral Flexion (Cm)	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	52	50	48	48	53
Mean	-0.16	0.41	0.94	0.28	0.49	0.48	1.29	1.72	1.48	1.46
SD	3.56	4.35	3.83	4.15	4.44	3.24	4.53	2.72	3.57	3.46
Median	0.32	1.18	1.00	0.55	0.55	1.06	1.44	1.75	1.72	1.50
Range	3.38	3.20	4.23	4.49	4.75	3.31	4.00	3.44	4.92	4.55
Minimum	-18.0	-11.3	-10.9	-18.0	-18.0	-9.75	-9.65	-7.57	-6.88	-6.88
Maximum	6.25	13.80	7.88	10.58	13.80	6.68	19.00	7.55	10.38	10.38
Lower 95% CI	-1.17	-0.83	-0.16	-0.92	-0.72	-0.42	0.01	0.93	0.44	0.50
Upper 95% CI	0.84	1.64	2.04	1.49	1.70	1.39	2.58	2.51	2.52	2.41
Wilcoxon paired-test(p-value)	0.7789	0.1569	0.0919	0.2318	0.2023	0.1034	0.0193	<0.0001	0.0054	0.0025

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Tragus to Wall Distance (cm) [Changes Per Visit From Baseline]: Changes in mean tragus to wall distance with respect to baseline values (16.04 cm in Treatment Group A and 15.01 cm in Treatment Group B were non significant at any time point for both treatment groups. At Week 2 mean changes (Table 29) in Treatment Groups A and B were -0.25 cm (1.6%) and -0.03 cm (0.2%), respectively. At Week 12 improvement was -0.42 (2.6%) in Treatment Group A and -0.33 (2.2%) in Treatment Group B.

Occiput to Wall Distance and Chest Expansion (Changes Per Visit From Baseline): Mean occiput to wall distance values were 4.55 cm and 3.86 cm for Treatment Groups A and Treatment Group B, respectively, at Baseline. For both treatment groups mean values (Table 30) improved at Week 2 and in the following visits. In general the differences were very similar among all weeks. However, in Treatment Group A, at Week 8 and last observation the mean differences were -0.81 cm (17.8%) and -0.72 cm (16.7%) clearly different to those of the remaining visits (0.33 cm, 7.3% at Week 2; 0.41 cm, 9% at Week 12). Those differences from both Week 8 and last observation were statistically significant, but not the values from the other weeks, compared to Baseline (Week 8: p=0.0367, CI 95 [-1.60, 0.01]; last observation: p=0.0380, CI 95 {-1.62, 0.17}).

In Treatment Group B, all values were not statistically significant with the exception of the Week 12 and last observation changes (Week 12: -0.46, 11.9% p=0.0389, CI 95 [-1.05, 0.12]; last observation:-0.42, 10.9%, p=0.0409, CI 95 {-0.95, 0.12}). When comparing both treatment groups non differences were detected.

For Treatment Groups A and B, mean chest expansion difference from Baseline (mean values at Baseline were 4.23 cm vs 4.01 cm) showed an improvement at Week 2 (Table 31) of 0.31 cm (7.3%) in Treatment Group A and. 0.30 cm (7.4%) in Treatment Group B, and in the following weeks the difference increased, reaching a maximum difference at Week 12 (1.05 cm, 24.8% vs 0.83 cm, 20.7%). Since Week 4 all changes were statistically significant. Again, there were not statistically significant differences between both arms of treatment.

Table 29. Tragus to Wall Distance (Cm) [Changes Per Visit From Baseline]

Tragus to Wall Distance (Cm)	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	48	46	47	46	51	51	49	48	48	53
Mean	-0.25	-0.16	-0.43	-0.42	-0.57	-0.03	-0.03	-0.37	-0.33	-0.30
SD	2.03	1.76	2.21	2.06	2.04	1.27	1.33	1.46	1.38	1.33
Median	0.00	0.00	0.00	0.00	-0.18	0.00	0.00	-0.20	0.00	0.00
Range	1.47	1.50	1.50	1.65	1.50	1.25	1.32	1.28	0.98	0.88
Minimum	-6.78	-5.75	-9.60	-7.50	-7.50	-3.45	-5.00	-5.20	-6.00	-6.00
Maximum	8.00	6.73	4.25	3.63	3.63	4.10	2.63	3.95	1.50	1.50
Lower 95% CI	-0.84	-0.69	-1.08	-1.03	-1.14	-0.39	-0.41	-0.80	-0.73	-0.67
Upper 95% CI	0.34	0.36	0.22	0.19	0.01	0.32	0.36	0.05	0.07	0.07
Wilcoxon paired-test(p-value)	0.2301	0.4348	0.2313	0.4788	0.1332	0.7357	0.7502	0.1042	0.2126	0.2215

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 30. Occiput-to-Wall Distance (Cm) [Changes Per Visit From Baseline]

Occiput-to-Wall Distance (Cm)	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	-0.33	-0.38	-0.81	-0.41	-0.72	-0.39	-0.14	-0.36	-0.46	-0.42
SD	2.15	2.74	2.75	3.05	3.29	2.72	1.38	1.68	2.04	1.95
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Range	0.25	1.00	1.25	1.13	1.50	0.00	0.00	1.00	1.00	1.00
Minimum	-7.00	-10.0	-9.00	-10.0	-11.0	-14.2	-4.50	-6.15	-6.25	-6.25
Maximum	4.75	11.00	5.50	12.50	12.50	4.75	3.25	5.00	8.00	8.00
Lower 95% CI	-0.94	-1.15	-1.60	-1.29	-1.62	-1.14	-0.52	-0.84	-1.05	-0.95
Upper 95% CI	0.27	0.40	-0.01	0.48	0.17	0.36	0.25	0.12	0.12	0.12
Wilcoxon paired-test(p-value)	0.3926	0.1941	0.0367	0.1622	0.0380	0.6147	0.6617	0.1113	0.0389	0.0409

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 31. Chest Expansion (Cm) [Changes Per Visit From Baseline]

Chest Expansion [Cm]	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	0.31	0.62	0.95	1.05	0.68	0.30	0.56	0.76	0.83	0.76
SD	1.95	1.83	2.46	2.11	2.79	1.50	1.69	1.93	2.03	1.97
Median	0.25	0.75	1.00	0.75	0.75	0.50	0.50	1.00	1.00	1.00
Range	1.75	1.50	1.60	2.25	2.25	1.25	1.50	2.00	2.25	2.50
Minimum	-7.00	-5.25	-4.50	-2.25	-11.0	-4.00	-3.50	-3.50	-4.25	-4.25
Maximum	6.00	5.00	13.50	9.50	9.50	5.00	6.25	5.75	5.25	5.25
Lower 95% CI	-0.24	0.10	0.24	0.44	-0.08	-0.11	0.09	0.21	0.25	0.22
Upper 95% CI	0.86	1.14	1.65	1.67	1.44	0.72	1.03	1.32	1.42	1.30
Wilcoxon paired-test(p-value)	0.1485	0.0023	0.0010	0.0004	0.0020	0.0750	0.0130	0.0097	0.0034	0.0034

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Joint Assessment (Changes Per Visit From Baseline): At Baseline, the mean of painful joints for Treatment Group A subjects was 3.28 (maximum and minimum values: 0-27) and 4.04 for Treatment Group B subjects (minimum and maximum values: 0-69). Table 32 shows reduction in the mean number of joints with pain was observed at Week 2 for both Treatment Groups A and B; -0.22 (minimum and maximum changes: -16.00, 45.00) and -1.96 (minimum and maximum changes: -32.00, 2.00). Maximum improvement was achieved at Week 12 for both Treatment Groups A and B with mean changes of -2.73 (minimum and maximum changes: -26.00, 5.00) and -2.18 (minimum and maximum changes: -30.00, 2.00). With the exception of the difference from Treatment Group A at Week 2, all changes were significant compared to baseline, but not between both groups of treatment.

With regard to the mean of swollen joints, an improvement was observed for both treatment groups since Week 2 and all the remaining time points. Table 33 shows in Treatment Group A the improvement was continued over the time, reaching a maximum improvement at Week 12 and last observation (-0.42 and -0.41). In Treatment Group A, all changes were not significant with the exception of last observation difference (p=0.0313). On the contrary, Treatment Group B subjects presented increases and reductions over the weeks. Indeed the maximum improvement was at Week 2 (-0.58) in comparison with improvement at Week 12 (-0.49) and last observation (-0.54). In Treatment Group B all changes were significant except differences at Week 8. The differences between both treatment groups were not significant.

No subjects experienced joint replacement during the trial. Of note, it is important to consider the very disparate values regarding joint evaluation which makes difficult to establish conclusions.

MASES Index (Changes Per Visit From Baseline): The mean number of enthesis with pain at Baseline and assessed by means of the MASES index (0-13) for Treatment Groups A and B were 2.85 and 2.46, respectively (Table 34). Both Groups improved at Week 2 with mean changes of -1.00 in Treatment Group A and -1.49 in Treatment Group B shows the improvement increased for both Groups in the following visits, achieving mean changes at Week 12 of -2.02 and -1.88 in Treatment Groups A and B. At last observation the differences were -1.94 and -1.89, respectively. All changes with respect to baseline were statistically significant, but not the comparison between Treatment Groups A and B.

Acute Phase Reactants (CRP and ESR; Changes Per Visit From Baseline): CRP values (Table 35) presented an important decrease as early at Week 4 for both groups of subjects. In the following weeks the values were quite similar. Overall, the mean reduction in CRP levels (mg/L) was higher than 11 mg/L (>50%) in both groups, reaching mean levels ≤10 mg/L, and the maximum decrease was reached at Week 8. All mean changes were statistically significant (p<0.0001) but not the comparison between Treatment Groups A and B.

Similarly to CRP, ESR mean (Table 36) decrease was detected at Week 4 in both groups. In Treatment Group A the mean reduction was rather similar at all weeks achieving a maximum decrease at Week 8 (-12.1 mm/h). However, in Treatment Group B the trend was different improving since Week 4 (-11.7 mm/h) until Week 12 in which the mean reduction was

-16.2 mm/h. Again, although all changes were statistically significant ($p<0.0001$) there were not differences when compared both arms of treatment.

SF-36 Questionnaire at Week 12 and Last Observation: Overall, both Groups improved regarding SF-36 evaluation at Week 12 and last observation compared to baseline. All items improved significantly with the exception of bodily pain. Bodily pain item, mean values at Baseline were 22.73 for Treatment Group A and 25.23 for Treatment Group B, worsened in both Groups showing mean changes of -1.39 (6.1%) and -1.91 (8.4%) at Week 12 and last observation in Treatment Group A while mean changes were -1.43 (6.3%) and -1.68 (6.7%) in Treatment Group B. These bodily pain changes were not significant.

Both physical (Baseline values: 33.37 and 30.23) and mental (Baseline values: 49.22 and 45.22) component summary scores showed important mean changes in both Groups at Week 12 (physical component summary score (PSC):13.40 (40.2%) and 15.05 (49.8%); mental component summary score (MSC): 10.51 (21.4%) and 10.38 (23%)) and last observation (PSC: 12.12 [36.37%] and 14.37 [47.5%]; MSC: 9.31 [18.9%] and 9.42 [20.8%]) in both groups, being statistically significant compared with mean values at Baseline ($p<0.0001$).

Table 37 shows the comparison between both groups was not statistically significant for any component of the SF-36 scale.

Table 32. Number of Joints With Pain (Changes Per Visit From Baseline)

Number of Joints With Pain	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	-0.22	-1.48	-2.53	-2.73	-2.56	-1.96	-1.96	-1.71	-2.18	-2.09
SD	7.25	5.82	6.03	6.09	5.77	5.13	4.82	4.16	5.45	5.29
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Range	2.00	3.00	3.00	4.00	3.00	2.00	2.00	2.00	2.00	2.00
Minimum	-16.0	-24.0	-27.0	-26.0	-26.0	-32.0	-26.0	-16.0	-30.0	-30.0
Maximum	45.00	19.00	5.00	5.00	5.00	2.00	4.00	10.00	2.00	3.00
Lower 95% CI	-2.25	-3.13	-4.26	-4.50	-4.13	-3.38	-3.32	-2.91	-3.75	-3.54
Upper 95% CI	1.82	0.17	-0.80	-0.96	-0.98	-0.55	-0.60	-0.52	-0.62	-0.65
Wilcoxon paired-test(p-value)	0.0660	0.0105	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	0.0003	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 33. Number of Joints With Swelling (Changes Per Visit From Baseline)

Number of Joints With Swelling	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	-0.27	-0.32	-0.39	-0.42	-0.41	-0.58	-0.49	-0.39	-0.49	-0.54
SD	1.33	1.45	1.44	1.47	1.41	2.55	2.40	2.52	2.58	2.57
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Range	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Minimum	-8.00	-6.00	-8.00	-8.00	-8.00	-18.0	-17.0	-17.0	-18.0	-18.0
Maximum	1.00	2.00	0.00	0.00	0.00	0.00	0.00	4.00	0.00	3.00
Lower 95% CI	-0.65	-0.73	-0.80	-0.84	-0.79	-1.29	-1.17	-1.11	-1.23	-1.24
Upper 95% CI	0.10	0.09	0.03	0.01	-0.02	0.12	0.19	0.34	0.25	0.16
Wilcoxon paired-test(p-value)	0.2500	0.2031	0.0625	0.0625	0.0313	0.0078	0.0156	0.2031	0.0313	0.0371

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 34. MASES Index (Changes Per Visit From Baseline)

MASES Index-Number of Enthesis With Pain	Treatment Group A					Treatment Group B				
	Week 2	Week 4	Week 8	Week 12	Last Observation	Week 2	Week 4	Week 8	Week 12	Last Observation
N	51	50	49	48	54	53	51	49	49	54
Mean	-1.00	-1.34	-1.47	-2.02	-1.94	-1.49	-1.67	-1.80	-1.88	-1.89
SD	2.28	2.12	2.02	2.56	2.48	2.50	2.45	2.49	2.75	2.78
Median	0.00	-1.00	-1.00	-1.00	-1.00	0.00	-1.00	-1.00	-1.00	-1.00
Range	2.00	3.00	3.00	4.50	4.00	2.00	3.00	3.00	3.00	3.00
Minimum	-5.00	-7.00	-7.00	-9.00	-9.00	-9.00	-10.0	-10.0	-10.0	-10.0
Maximum	8.00	3.00	2.00	4.00	4.00	2.00	1.00	1.00	1.00	1.00
Lower 95% CI	-1.64	-1.94	-2.05	-2.77	-2.62	-2.18	-2.35	-2.51	-2.67	-2.65
Upper 95% CI	-0.36	-0.74	-0.89	-1.28	-1.27	-0.80	-0.98	-1.08	-1.09	-1.13
Wilcoxon paired-test(p-value)	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; MASES = Masstrich index; N = number of subjects; SD = standard deviation.

Table 35. C Reactive Protein(mg/L) [Changes Per Visit From Baseline]

C Reactive Protein(mg/L)	Treatment Group A				Treatment Group B			
	Week 4	Week 8	Week 12	Last Observation	Week 4	Week 8	Week 12	Last Observation
N	43	45	45	51	46	44	44	50
Mean	-10.9	-12.4	-11.6	-10.4	-12.3	-13.6	-11.7	-11.9
SD	15.33	17.99	18.42	20.25	22.05	24.45	21.44	20.68
Median	-7.90	-8.00	-6.52	-7.00	-4.15	-5.40	-5.25	-5.25
Range	11.50	13.00	11.90	13.00	12.80	8.80	8.55	8.90
Minimum	-58.5	-101	-99.0	-99.0	-107	-115	-109	-109
Maximum	19.60	7.00	13.50	61.00	14.40	5.80	16.40	16.40
Lower 95% CI	-15.7	-17.8	-17.1	-16.1	-18.9	-21.1	-18.2	-17.7
Upper 95% CI	-6.21	-7.00	-6.08	-4.71	-5.77	-6.19	-5.20	-5.98
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; N = number of subjects; SD = standard deviation.

Table 36. ESR(mm/h) [Changes Per Visit From Baseline]

ESR (mm/h)	Treatment Group A				Treatment Group B			
	Week 4	Week 8	Week 12	Last Observation	Week 4	Week 8	Week 12	Last Observation
N	47	48	47	53	43	45	46	50
Mean	-10.7	-12.1	-11.8	-11.8	-11.7	-13.7	-16.2	-15.2
SD	17.15	16.04	14.47	14.28	14.23	15.90	16.06	16.16
Median	-7.00	-9.00	-10.0	-10.0	-7.00	-9.00	-10.5	-10.5
Range	18.00	13.00	14.00	14.00	18.00	20.00	21.00	21.00
Minimum	-62.0	-65.0	-58.0	-58.0	-58.0	-57.0	-68.0	-68.0
Maximum	27.00	24.00	25.00	25.00	16.00	30.00	16.00	16.00
Lower 95% CI	-15.7	-16.8	-16.0	-15.7	-16.0	-18.4	-21.0	-19.8
Upper 95% CI	-5.67	-7.49	-7.52	-7.86	-7.27	-8.89	-11.4	-10.6
Wilcoxon paired-test(p-value)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; ESR = erythrocyte sedimentation rate; N = number of subjects; SD = standard deviation.

Table 37. PSC and MSC Scores (SF-36)- Mean Changes From Baseline at Week 12 and Last Observation

Variable	Treatment Group A	Treatment Group B
PSC change at Week 12, mean, (95% CI)	13.40 (7.87, 18.93)	15.05 (10.77, 19.33)
PSC change at last observation, mean, (95% CI)	12.12 (7.01, 17.23)	14.37 (10.14, 18.60)
MSC change at Week 12, mean, (95% CI)	10.51 (6.49, 14.54)	10.38 (5.93, 14.84)
MSC change at last observation, mean, (95% CI)	9.31 (5.64, 12.99)	9.42 (4.98, 13.87)

A = 50 mg twice in a week; B = 50 mg once in a week; CI = confidence interval; MSC = mental component summary score; PSC = physical component summary score.

Euro Qol questionnaire at Week 12 and last observation: EuroQol index showed mean improvements with respect to Baseline (mean values of 0.47 and 0.48 at Baseline) of 0.22 and 0.20 at Week 12 and last observation in Group A while the improvements in Treatment Group B were 0.20 and 0.20 at the same time points. All changes were statistically significant compared to baseline ($p<0.0001$). The comparison between Treatment Groups A and B was not statistically significant at Week 12 and at last observation. Regarding the items comprising EuroQol scale and evaluating values along visits, there were significant changes in Treatment Group A in mobility, self-care, usual activities, but not in pain discomfort and anxiety depression. In Treatment Group B all items improved significantly except usual activities and anxiety depression.

When compared both groups, there were statistically significant differences with regard to pain-discomfort item. At Week 12, 89.36% of subjects referred pain-discomfort problems compared to 73.47% in Treatment Group B ($p=0.0461$). Very similar results were observed at last observation for each Group (90.57% vs 75.00%; $p=0.0343$). The Groups comparison in the remaining items was not significant.

Similarly to EuroQol index, results from EuroQol VAS in Treatment Group A showed improvements of 23.52 and 23.54 at Week 12 and last observation. In Treatment Group B the mean improvements were 22.55 at Week 12 and 21.08 at last observation. Again, although the improvements were significant ($p<0.0001$) there was not the comparison of the groups.

Overall, the rates of response in this trial were very similar to that observed in previous 50 mg ETN 12 weeks trials.

Safety Results:

Serious Adverse Events (SAEs): One (1) subject from Treatment Group A and 2 from Treatment Group B reported SAEs during the course of the trial; which were severe although they were resolved and were not life-threatening; details are presented in Table 38.

Table 38. Serious Adverse Events

Serial Number	Age	Race	Sex	Treatment Group	Number of Doses, Duration and Last Dose of Treatment Before SAE	Event Term (MedDRA Version 10.0, Preferred Term)	Duration of SAE	Severity	Action Taken	Outcome	Causality
1	48	White	female	B	16 53 days 06-aug-2007	Diarrheic syndrome	20 days	Severe	Withdrawn	Resolved	Related
2	57	White	male	A	4 9 days 07-sep-2007	Diarrhea, abdominal pain and distension	09 days	Severe	Treatment stopped and reintroduced later	Resolved	Related
3	58	White	female	B	7 21 days 20-dec-2007	Viral respiratory infection	60 days	Severe	Withdrawn	Resolved	Related

A = 50 mg twice in a week; B = 50 mg once in a week; MedDRA = medical dictionary for drug regulatory activities; SAE = serious adverse event.

Adverse Events: All AEs were mild (86.1%) or moderate (8.9%); the proportion (101 AEs, 51 in Treatment Group A and 50 in Treatment Group B) and type of AEs reported for both groups were quite similar. By system organ class the majority of AEs were those related to infections and infestations (20.37% vs 25.93% for Treatment Groups A and B, respectively; nasopharyngitis/upper respiratory tract injection and pharyngitis), gastrointestinal disorders (18.52% vs 7.41% for Treatment Groups A and B, respectively; abdominal pain, and diarrhea), general disorders and administration site conditions (12.96% vs 18.52% for Treatment Groups A and B, respectively; injection site reactions), and investigations (7.41% vs 10% for Treatment Groups A and B, respectively; transaminases increased).

The summary of all AEs and summary of treatment-related AEs are presented in Table 39 and Table 40 respectively. The most common treatment-emergent adverse event was injection site reaction with rates of 13.0% in Treatment Group A and 14.8% in Treatment Group B. In Treatment Group A, 25 AEs were related to the study treatment while in Treatment Group B there were 18. Details are presented in Table 41.

Table 39. Summary of All AEs

System Organ Class MedRA Preferred Term	Treatment Group A N=54	Treatment Group B N=54
	n	n
Ear and labyrinth disorders		
Vertigo		1
Conjunctivitis		1
Uveitis	1	
Gastrointestinal disorders		
Abdominal distension	1	
Abdominal pain	2	1
Abdominal pain upper	2	
Constipation	1	2
Diarrhea	1	
Flatulence	1	
Esophageal spasm	1	
Retching	1	1
Vomiting		1
General disorders and administration site conditions		
Asthenia		1
Feeling abnormal		1
Injection site erythema		1
Injection site induration		1
Injection site inflammation		1
Injection site reaction	2	1
Local reaction	1	
Puncture site reaction	4	4
Infections and infestations		
Cellulitis		1
Folliculitis	1	
Furuncle	1	
Gastroenteritis	1	
Herpes simplex	1	
Hordeolum		1
Nasopharyngitis	2	6
Pharyngitis		2
Pharyngotonsillitis	1	
Respiratory tract infection viral		1
Rhinitis		1
Tinea versicolour	1	
Upper respiratory tract infection	3	2
Injury, poisoning and procedural complications		
Muscle rupture	1	
Procedural dizziness	1	2
Procedural headache	1	
Wound	1	
Investigations		
Alanine aminotransferase increased		1
Bilirubin conjugated increased		1
Transaminases	3	2
Transaminases increased	1	2
Metabolism and nutrition disorders		
Anorexia		1

Table 39. Summary of All AEs

System Organ Class MedRA Preferred Term	Treatment Group A N=54	Treatment Group B N=54
	n	n
Musculoskeletal and connective tissue disorders		
Arthralgia	2	1
Bone disorder	1	
Muscle contracture	1	
Nervous system disorders		
Dizziness	2	
Headache	2	1
Somnolence	1	
Psychiatric disorders		
Anxiety	1	
Insomnia	1	1
Reproductive system and breast disorders		
Amenorrhea		1
Haematospermia	1	
Prostatitis	1	
Respiratory, thoracic and mediastinal disorders		
Cough		1
Skin and subcutaneous tissue disorders		
Eczema		1
Rash erythematous		1
Urticaria		1
Surgical and medical procedures		
Inguinal hernia repair	1	
Tooth extraction		1
Vascular disorders		
Hypotension		1
Pallor		1
Total	51	50

A = 50 mg twice in a week; AE = adverse event; B = 50 mg once in a week;
MedRA = medical dictionary for drug regulatory activities; n = number of subjects with specified criteria;
N = number of subjects.

Table 40. Summary of Treatment-Related AEs

System Organ Class MedRA Preferred Term	Treatment Group A N=54	Treatment Group B N=54
	n	n
Gastrointestinal disorders		
Abdominal distension	1	
Abdominal pain	1	
Abdominal pain upper	1	
Diarrhea	1	1
Flatulence	1	
General disorders and administration site conditions		
Injection site erythema		1
Injection site induration		1
Injection site inflammation		1
Injection site reaction	2	1
Local reaction	1	
Puncture site reaction	4	4
Infections and infestations		
Cellulitis		1
Folliculitis	1	
Furuncle	1	
Nasopharyngitis	1	2
Pharyngitis		1
Respiratory tract infection viral		1
Tinea versicolour	1	
Upper respiratory tract infection	2	
Injury, poisoning and procedural complications		
Procedural dizziness	1	
Procedural headache	1	
Nervous system disorders		
Dizziness	1	
Headache	1	
Somnolence	1	
Psychiatric disorders		
Anxiety	1	
Insomnia	1	
Reproductive system and breast disorders		
Amenorrhea		1
Skin and subcutaneous tissue disorders		
Eczema		1
Rash erythematous		1
Urticaria		1
Total	25	18

A = 50 mg twice in a week; AE = adverse event; B = 50 mg once in a week;
MedRA = medical dictionary for drug regulatory activities; n = number of subjects with specified criteria;
N = number of subjects.

Table 41. TEAEs (>3%)

System Organ Class	AE	Treatment Group A		Treatment Group B	
		Related	Unrelated	Related	Unrelated
General disorders and administration site conditions	Injection site reactions	7 (13.0%)	0	8 (14.8%)	0
Infections and infestations	Nasopharyngitis/Upper respiratory tract infection	3 (5.56%)	2 (3.70%)	2 (3.70%)	6 (11.10%)
	Pharyngitis	0	0	1 (1.85%)	1 (1.85%)
Gastrointestinal disorders	Abdominal pain	1 (1.85%)	1 (1.85%)	0	0
	Diarrhea	1 (1.85%)	0	1 (1.85%)	1 (1.85%)
Investigations	Transaminases increased	0	4 (7.40%)	0	4 (7.40%)
Injury, poisoning and procedural complications	Procedural dizziness	1 (1.85%)	0	0	2 (3.70%)
Nervous system disorders	Dizziness	1 (1.85%)	1 (1.85%)		

A = 50 mg twice in a week; AE = adverse event; B = 50 mg once in a week; TEAEs = treatment-emergent AEs.

Discontinuations due to Adverse Events: In Treatment Group B 2 subjects were discontinued from the study due to AEs. One (1) subject was reported as diarrheic syndrome and another subject reported as viral respiratory infection. There were no discontinuations from the study due to AEs in Treatment Group A.

Deaths: No deaths were reported during the study.

Other Safety Results: There were no cases of opportunistic infections, malignancies, multiple sclerosis, demyelination and lupus during the trial. There were no unexpected safety findings.

Vital Signs and Physical Findings: There were no clinically relevant findings regarding vital signs, blood pressure and pulse rate, during the study.

CONCLUSION: In conclusion and in spite of the small size of the trial and the absence of a Placebo Group, the results of this trial support the safety and efficacy of both Treatments A and B as early as 2 weeks and over 12 weeks to treat active AS in subjects who have failed to standard treatments, being both treatments equally effective.