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

PROTOCOL NO.: 0881A3-4458 (B1801008)

PROTOCOL TITLE: Effects of Etanercept on Endothelial Function and Carotid Intima-Media Thickness in Patients With Active Ankylosing Spondylitis: a 52 Weeks, Randomized, Double Blind, Placebo-Controlled Study

Study Centers: Four (4) study centers in Italy took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 19 January 2010 to 10 November 2011. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives:

Primary objective:

- To evaluate the effects of etanercept on endothelial function and intima-media thickness (IMT) in subjects with ankylosing spondylitis (AS) at 12 weeks

Secondary objectives:

- To evaluate sustained effect of etanercept on endothelial function and IMT in subjects with AS at 52 weeks
- To evaluate the effect of etanercept on AS disease activity over 12 and 52 weeks
- To evaluate the safety of etanercept in AS subjects over 12 and 52 weeks

METHODS

Study Design: This was a randomized, double blind, active-placebo, parallel design, outpatient, multicenter study in subjects with AS. Screening of subjects occurred up to 4 weeks prior to randomization followed by a treatment phase of 52 weeks. Subjects were randomized to treatment with etanercept 50 mg subcutaneously (SC) once a week or etanercept placebo SC once a week, in a 1:1 allocation, respectively. After 12 weeks of treatment, those subjects who maintained active disease (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4) despite treatments were classified as early discontinuations and were allocated to other treatments commercially available. Subjects that received at least 1 dosage of the study drug were considered in the final analysis as per

the intention to treat method. The different assessments scheduled at each visit (Baseline, 4, 12, 24, 36 and 52 Weeks and in case of early discontinuation) are presented in Table 1.

Table 1. Schedule of Assessments

Study Week	Screening[a] -4 to 0	Baseline 0	4	12	24	36	52	Early Discontinuation
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Informed Consent	X							
Medical History	X							
Pelvic X-ray[b]	X							
Chest X-ray[b]	X							
Inclusion/Exclusion Criteria	X	X						
Prior Medications	X[c]	X[d]						
Randomization		X						
HLA-B27[e]		X						
Concomitant Medications			X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X
Smoking attitude	X							
Body Mass Index (BMI)	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X
Joint Assessment[g]	X	X[h]	X	X	X	X	X	X
Physician Global Assessment of disease activity[g]	X	X[h]	X	X	X	X	X	X
BASMI[g]	X	X[h]	X	X	X	X	X	X
Occiput-To-Wall Distance[g]	X	X[h]	X	X	X	X	X	X
Chest Expansion[g]	X	X[h]	X	X	X	X	X	X
Patient Global Assessment of disease activity	X	X[h]	X	X	X	X	X	X
Nocturnal and Total Back Pain	X	X[h]	X	X	X	X	X	X
BASFI	X	X[h]	X	X	X	X	X	X
BASDAI	X	X[h]	X	X	X	X	X	X
Electrocradiogram (ECG)	X							
Pregnancy Test[i]	X	X						
Urinalysis	X	X[h]						X
Chemistry and Haematology[j]	X	X[h]	X	X	X	X	X	X
CRP	X	X[h]	X	X	X	X	X	X
Erythrocyte Sedimentation Rate (ESR)	X	X[h]	X	X	X	X	X	X
FMD	X	X	X	X	X	X	X	X
IMT	X	X		X			X	X
AE[k]		X	X	X	X	X	X	X

Table 1. Schedule of Assessments

Study Week	Screening[a] -4 to 0	Baseline 0	4	12	24	36	52	Early Discontinuation
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Drug Accountability			X	X	X	X	X	X
Dispense diary card		X	X	X	X	X		
Dispense study drug[l]		X	X	X	X	X		

AE = adverse event; BASMI = Bath Ankylosing Spondylitis Metrology Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-Reactive Protein; FMD = Flow-Mediated Dilatation; HLA-B27 = Human Leukocyte Antigen B27; IMT = intima media thickness.

a. 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.
b. Waived if within 12 weeks and report was available and was included in subject's source documents.
c. Reporting of medications received within 28 days prior to screening.
d. Reporting of medications since screening visit.
e. Waived if results were known and a copy of laboratory report was in source documents.
f. Included sitting blood pressure, pulse rate and weight; height was recorded only at baseline.
g. It was recommended that the same qualified medical personnel completed these assessments at each visit.
h. Waived if first dose within 14 days of screening evaluation.
i. For women of childbearing potential only (serum test at screening visit, urine at baseline visit).
j. The total volume of blood collected from each subject was approximately 110 to 130 mL for the study.
k. Follow up telephone call to assess new and ongoing AEs was conducted approximately 15 days after Visit 7 or early discontinuation.
l. First dose administered after baseline evaluations were completed.

Number of Subjects (Planned and Analyzed): The study planned to enroll about 40 subjects per arm. Subjects withdrawn from the study were not replaced, regardless of the reason for withdrawal. In total 51 subjects were enrolled into the study and 34 were randomized (18 in the etanercept group and 16 in the placebo group). All randomized subjects received at least 1 dose of study drug and were then part of the safety set.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged ≥18 years, with a diagnosis of AS defined by Modified New York Criteria for Ankylosing Spondylitis and an active disease defined by BASDAI ≥4 at screening visit. Subjects capable of complying with the treatment schedule and doses throughout the 52 weeks, agreeing with the use of reliable methods of birth control for the duration of the study and able to self-inject drug and store study drug at 2-8ºC.

Study Treatment: All subjects received SC injections once weekly for 52 weeks with either etanercept 50 mg or matching placebo. The sponsor supplied individual subject packages containing 50 mg etanercept pre-filled syringes and 50 mg non-active ingredients in placebo pre-filled syringes. Etanercept or matching placebo had to be administered at approximately the same time of day (±4 hours) and on the same day of the week. Injections had to be administered in the abdomen, thigh, or upper arm. The location of injections had to be rotated with each dose.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Mean change in Flow-Mediated Dilatation (FMD) from baseline to 12 weeks. Primary objective was the assessment of endothelial function, as per FMD in subjects with active AS at 12 weeks. Particularly, it was evaluated any positive variation of FMD in AS subjects, after and during etanercept treatment, comparing placebo controls

Secondary Efficacy Endpoints:

- Mean change in FMD, IMT values, and blood tests from baseline to Weeks 4, 12, 24, 36, and 52
- Mean change in IMT values from baseline to Weeks 12 and 52
- Mean change in IMT and blood tests (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], serum homocysteine) from baseline to 12 weeks
- Mean change in BASDAI score from baseline to Weeks 4, 12, 24, 36, and 52
- Proportion of subjects achieving BASDAI 50 improvement at Weeks 4, 12, 24, 36, and 52
- Proportion of subjects achieving assessment in ankylosing spondylitis (ASAS)20, ASAS40, ASAS50, ASAS70, ASAS 5/6, and partial remission at Weeks 4, 12, 24, 36, and 52

- Change from baseline by visit in the spinal mobility as measured by Bath Ankylosing Spondylitis Metrology Index (BASMI) and its components, occiput-to-wall distance, and chest expansion.

Safety Evaluations: Safety of etanercept was assessed by evaluation of adverse events (AEs), serious adverse events (SAEs), vital signs (blood pressure, heart rate), physical examination, results of laboratory testing and premature withdrawal. Safety variables were assessed throughout the course of the study (Table 1). Safety data up to approximately 15 days (or date of follow-up telephone call) after the 52 weeks of treatment were collected.

Statistical Methods:

Analysis Sets: The modified Intent-To-Treat (mITT) set was defined as all randomized subjects who received at least 1 dose of study drug after randomization and who had at least 1 available evaluation after the first administration of study drug after randomization. All subjects who received at least 1 dose of study drug were included in safety analyses (safety set).

All analyses were performed on the mITT set.

The repeated measures analysis of the effect of etanercept administration on quantitative parameters change from baseline was performed using a Mixed Model for Repeated Measures (MMRM). Analyses included the fixed, categorical effects of treatment, visit (Week 4 and Week 12), and treatment-by-visit interaction, as well as the continuous, fixed covariates of the baseline value and baseline-by-visit interaction. An unstructured covariance matrix was used to model the within-subject errors. If the model with the unstructured covariance matrix failed to converge, other covariance structures including Toeplitz, compound symmetry, and spatial power were considered. The covariance structure converging to the best fit, as determined by Akaike's information criterion, was used as the primary analysis. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Least squares means, p-value and 2-sided 95% Confidence Intervals (CIs) of the treatment difference were determined. Both between-group and within group comparisons were provided. Significance tests were based on least-squares means using a 2-sided α =0.05.

The primary hypothesis was that the effect of etanercept on endothelial function as measured by FMD in AS subjects would be different from the effect of a placebo control. The change in FMD from baseline to 12 weeks (primary endpoint) was compared in AS subjects between etanercept and placebo controls. Statistical testing, unless otherwise stated, was 2-sided and used the 5% significance level in accordance with standard practice.

As a sensitivity analysis, the effect of etanercept administration on FMD change from baseline was assessed using the MMRM adjusted on location of FMD measurement. In addition, the analysis was repeated excluding the data from site 8, as a sensitivity analysis, due to concerns relating to change in equipment for measurement of FMD at this site. For some efficacy endpoints analyzed using the MMRM, the hypothesis of normal distribution of residuals was questionable. A sensitivity analysis excluding outliers was then added that respected the normal distribution hypothesis.

- The IMT (values and changes from baseline value) were described at all available time-points (Screening, Baseline, Week 12 and Week 52) by treatment group and overall. The changes from Baseline to week 12 were analyzed using an ANalysis of COVAriance (ANCOVA) with treatment as fixed factor and baseline as covariate.

- A full description of the values at each time-point (Screening, Baseline and Week 4 to Week 52) and changes from baseline were provided by treatment group and overall for ESR, plasma CRP, total cholesterol, LDL, HDL, triglycerides, and total homocysteine.

- The BASDAI score and its components were fully described at each time-point (Screening, Baseline and Week 4 to Week 52) by treatment group and overall. The BASDAI score changes from baseline were also provided. The BASDAI score changes from baseline to week 4 and week 12 were analyzed using the MMRM.

- The proportion of subjects achieving BASDAI 50 improvement at each time-point (Week 4 to Week 52) was described by treatment group and overall.

- The ASAS20, ASAS40, ASAS50, ASAS70 and ASAS 5/6 response rates, and the partial remission rate using the dichotomous response Yes/No, were described at each time point (Screening, Baseline and Week 4 to Week 52) by treatment group.

- The BASMI score, the occiput-to-wall distance and the chest expansion were fully described (values and changes from baseline value) at each time-point (screening, baseline and Week 4 to Week 52) by treatment group and overall. The changes from baseline were analyzed using the MMRM.

- Summaries at each time-point (Screening, Baseline and Week 4 to Week 52) with values and changes from baseline were provided by treatment group and overall for the following parameters:

- Number of tender and swollen joints,

- Physician global assessments of disease activity,

- Subject global assessments of disease activity,

- Nocturnal and total back pain,

- Bath ankylosing spondylitis functional index (BASFI) score and its components.

Due to the early termination of the study with very few subjects attending visits after week 12, analyses planned in the protocol were restricted. In particular, analyses were limited to Week 12 and planned sensitivity and per-protocol analyses were dropped.

RESULTS

Subject Disposition and Demography: The subject disposition and primary reason for withdrawal from the study are presented in Table 2. A total of 29 subjects were prematurely

withdrawn from the study. The main reasons for discontinuation were unsatisfactory response (15 subjects, 52%) and discontinuation of study by sponsor (10 subjects, 34%).

Table 2. Subject disposition

Conclusion Status Reason	Etanercept	Placebo	Total
Assigned to Treatment	18	16	34
Treated	18	16	34
Completed	0	3	3
Discontinued (mITT set), n (%)	17 (100%)	12 (80%)	29 (91%)
Unsatisfactory response - Efficacy	6 (35%)	9 (75%)	15 (52%)
Adverse event	1 (6%)	1 (8%)	2 (7%)
Subject request	1 (6%)	-	1 (3%)
Discontinuation of study by sponsor	8 (47%)	2 (17%)	10 (34%)
Protocol violation	1 (6%)	-	1 (3%)
Analyzed for Efficacy (mITT)[a]	17	15	32
Analyzed for Safety	18	16	34

mITT = modified intent-to-treat; n = number of subjects in each treatment group..

a. Two subjects had no evaluation after the first injection and were excluded from the mITT set.

For the mITT set, the demographic and other baseline characteristics were mainly comparable between randomization groups. Overall subjects aged from 25 to 69 years and the mean age at screening was 40.3 (±8.2) years in the etanercept group and 45.6 (±12.6) years in the placebo group (Table 3). The gender distribution was 53% men and 47% women in the etanercept group and 33% men and 67% women in the placebo group.

Table 3. Demographic and Baseline Characteristics – mITT Set

Characteristic	Etanercept n=17	Placebo n=15	Total n=32
Age (years)			
Mean (SD)	40.3 (8.2)	45.6 (12.6)	42.8 (10.7)
Gender			
Men	9 (53%)	5 (33%)	14 (44%)
Women	8 (47%)	10 (67%)	18 (56%)
BMI (kg/m²)			
Mean (SD)	24.9 (5.3)	25.1 (4.5)	25.0 (4.8)
Assessment of AS:			
Flow-mediated dilatation result (%)			
Mean (SD)	10.1 (5.9)	13.4 (7.7)	11.6 (6.9)
Maximum flow-mediated dilatation result (mm)			
Mean (SD)	3.1 (2.2)	2.7 (1.8)	2.9 (2.0)
Intima-media thickness results (mm)			
Common carotid artery			
Mean (SD)	0.7 (0.2)	0.8 (0.1)	0.7 (0.2)
Missing data	0	1	1
Common bulb			
Mean (SD)	0.8 (0.2)	0.9 (0.2)	0.8 (0.2)
Missing data	0	1	1
Internal carotid artery			
Mean (SD)	0.7 (0.2)	0.8 (0.3)	0.7 (0.3)
Missing data	0	1	1
BASMI score (the higher this score is, the more severe the subject's limitation of movement due to AS is)			
Mean (SD)	3.5 (2.2)	4.0 (2.5)	3.7 (2.3)
Occiput-to-wall distance (cm)			
Mean (SD)	7.7 (4.0)	9.8 (5.7)	8.7 (4.9)
Chest expansion (cm)			
Mean (SD)	4.7 (2.2)	4.5 (1.7)	4.6 (2.0)
Physician global assessment of disease activity (VAS 100 mm: 0 – none to 100 – severe)			
Mean (SD)	68.6 (15.1)	66.7 (13.7)	67.8 (14.3)
Subject global assessment of disease activity (VAS 100 mm: 0 – none to 100 – severe)			
Mean (SD)	66.4 (21.6)	63.9 (18.8)	65.2 (20.0)
Nocturnal back pain (VAS 100 mm: 0 – no pain to 100 – most severe pain)			
Mean (SD)	62.3 (30.0)	59.6 (22.3)	61.0 (26.3)
Total back pain (VAS 100 mm: 0 – no pain to 100 – most severe pain)			
Mean (SD)	66.2 (19.5)	66.8 (16.5)	66.5 (17.9)

AS = ankylosing spondylitis; BASMI = bath ankylosing spondylitis metrology index; BMI = body mass index; mITT = modified intent-to-treat; SD = standard deviation; VAS = visual analog scale.

Efficacy Results:

Flow-Mediated Dilation: Mean change in FMD between baseline and Week 12 was 4.1% (±11.4) in the etanercept group and 0.3% (±7.4) in the placebo group. The FMD is described in the mITT set in Table 4.

Table 4. Flow-Mediated Dilatation (%) – mITT Set

Time	Etanercept n=17	Placebo n=15	Total n=32
Baseline			
Mean (SD)	10.1 (5.9)	13.4 (7.7)	11.6 (6.9)
Week 4			
Mean (SD)	12.7 (6.9)	13.2 (8.2)	12.9 (7.4)
Missing data	0	2	2
Change from baseline to Week 4			
Mean (SD)	2.6 (9.5)	-0.7 (4.7)	1.2 (7.9)
Missing data	0	2	2
Week 12			
Mean (SD)	14.1 (12.3)	13.9 (5.3)	14.0 (9.8)
Missing data	1	3	4
Change from baseline to Week 12			
Mean (SD)	4.1 (11.4)	0.3 (7.4)	2.5 (9.9)
Missing data	1	3	4

mITT = modified intent-to-treat; SD=standard deviation.

The adjusted mean difference (2-sided 95% CI) between the 2 groups (etanercept - placebo) at Week 12 was 1.72 (-5.14; 8.58) in the primary analysis and -0.64 (-4.72; 3.43) in the sensitivity analysis excluding outliers. Thus no statistically significant difference between the 2 groups was shown.

Results of other sensitivity analyses, first adjusted for measurement location and then excluding 1 site with forearm measurements, were similar to those obtained for the primary analysis and no statistically significant difference between the 2 groups was observed.

Mean change in maximum FMD between Baseline and Week 12 was 0.12 mm (±0.57) in the etanercept group and 0.38 mm (±1.12) in the placebo group.

Secondary criteria:

None of the planned analyses at Week 52 were presented, due to small numbers of subjects with evaluable values (3 subjects in the placebo group who completed the study and 4 subjects in the etanercept group with valid values despite premature discontinuation).

Intima-Media Thickness: Mean change in IMT (mITT set) between baseline and Week 12 was 0.00 mm (±0.15) in the etanercept group and -0.09 mm (±0.16) in the placebo group for the common carotid artery. It was -0.03 mm (±0.11) in the etanercept group and -0.02 mm (±0.12) in the placebo group for the common bulb and -0.03 mm (±0.16) in the etanercept group and -0.07 mm (±0.28) in the placebo group for the internal carotid artery.

Only a significant decrease of 0.06 mm for the IMT of the common carotid artery in the etanercept group when performing the sensitivity analysis excluding outliers was noted (p=0.012).

The adjusted mean differences (2-sided 95% CI) between the 2 groups (etanercept - placebo) at Week 12 were 0.02 (-0.08; 0.13) and -0.04 (-0.11; 0.04) for the common carotid artery

(main and sensitivity analyses), -0.03 (-0.13; 0.07) for the common bulb and -0.03 (-0.14; 0.08) for the internal carotid artery. No difference in IMT between the 2 groups was observed.

Blood Tests: Between baseline and Week 12, the mean ESR and plasma CRP decreased by 29.5 mm/hour (±36.8) and 11.8 mg/L (±19.5) respectively in the etanercept group while both were quite stable in the placebo group (changes of 4.4 mm/hour [±17.4] for ESR and change of 2.0 mg/L [±6.2] for CRP).

In both groups, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and total homocysteine remained quite stable between baseline and Week 12, with overall mean changes of 0.14 mmol/L (±0.64), 0.16 mmol/L (±1.02), 0.03 mmol/L (±0.18), 0.06 mmol/L (±0.61) and 0.02 µmol/L (±3.21) respectively.

Bath Ankylosing Spondylitis Disease Activity Index: In the etanercept group, the adjusted mean changes from baseline indicated a significant decrease of the BASDAI score at Week 4 and Week 12: -1.8 points ($p=0.002$) and -3.2 points ($p<0.001$) respectively. Adjusted mean changes were not significantly different from 0 in the placebo group.

The adjusted mean differences (2-sided 95% CI) between the 2 groups (etanercept - placebo) were significantly different from 0 at Week 4 and at Week 12, -1.77 (-3.05; -0.50) and -2.02 (-3.70; -0.33) respectively, indicating a less disabling AS in the etanercept group.

At Week 12, more subjects in the etanercept group than in the placebo group achieved an improvement in BASDAI score of at least 50%: 10 subjects (63%) and 3 subjects (23%) respectively.

Assessment in Ankylosing Spondylitis: Up to Week 12, ASAS20 was achieved by 11 subjects (69%) in the etanercept group and 6 subjects (50%) in the placebo group. The proportion of subjects achieving ASAS40, ASAS50, ASAS70 and ASAS5/6 up to Week 12 was 56% and 42%, 56% and 25%, 31% and 8% and 31% and 0% in the etanercept and placebo groups respectively.

The proportion of subjects of the mITT set who achieved ASAS20, ASAS40, ASAS50, ASAS70 and ASAS5/6 up to week 12 is presented in Table 5.

Table 5. ASAS Response Rates up to Week 12 – mITT Set

Response rate	Etanercept n=17	Placebo n=15	Total n=32
Missing data	1	3	4
ASAS20	11 (69%)	6 (50%)	17 (61%)
ASAS40	9 (56%)	5 (42%)	14 (50%)
ASAS50	9 (56%)	3 (25%)	12 (43%)
ASAS70	5 (31%)	1 (8%)	6 (21%)
ASAS5/6	5 (31%)	-	5 (18%)

ASAS = assessment in ankylosing spondylitis; mITT = modified intent-to-treat; n = number of subjects in each treatment group.

The proportion of subjects who achieved partial remission was 47% and 39% in the etanercept and placebo groups respectively.

Bath Ankylosing Spondylitis Metrology Index: The adjusted mean changes from baseline indicated a significant decrease of the BASMI score of 0.73 point (p=0.024) at Week 12 in the etanercept group and a significant increase of the BASMI score of 0.64 point (p=0.018) at Week 4 in the placebo group.

The adjusted mean differences (2-sided 95% CI) between the 2 groups (etanercept - placebo) were significantly different at Week 4, -1.07 (-1.74; -0.40) and at Week 12, -0.91 (-1.72; -0.10), indicating a better improvement in subject's limitation of movement due to AS in the etanercept group.

In both groups, occiput-to-wall distance and chest expansion remained quite stable between baseline and Week 12. Conclusions of main and sensitivity analyses differed, thus no statistically significant difference between the 2 groups was shown.

In both groups, the number of tender and swollen joints remained quite stable between baseline and Week 12, with median change equal to 0 in both groups.

Physician and subject global assessment of disease activity, measured on a 0 (no activity) to 100 (severe activity) scale, both decreased between baseline and Week 12. Improvement was greater in the etanercept group than in the placebo group:
-36.0 points (±28.8) vs. -13.0 points (±27.4) for the physician assessment and -31.6 points (±28.4) vs. -12.6 points (±24.4) for the subject assessment.

In the same way, nocturnal and total back pain, measured on a 0 (no pain) to 100 (most severe pain) scale, both decreased between baseline and Week 12. Improvement was greater in the etanercept group than in the placebo group: -29.8 points (±35.3) vs. -14.9 points (±24.8) for the nocturnal back pain and -32.8 points (±29.6) vs. -19.3 points (±29.1) for the total back pain.

In the etanercept group, a mean decrease of 1.8 points (±2.1) in the BASFI score indicated that subjects felt less functionally impaired at Week 12 than at baseline, while in the placebo group the mean BASFI score was quite stable with a decrease of 0.4 points (±1.4).

Safety Results: The study was prematurely terminated and safety results are available for only 34 subjects: 18 in the etanercept group and 16 in the placebo group.

A summary of the treatment-emergent adverse events (TEAEs) is presented in Table 6. TEAEs were defined as events that emerged during treatment (from the first injection of study drug) and up to 15 days after the last date of study drug administration. In the etanercept group, 9 subjects (50%) experienced a total of 20 TEAEs. In the placebo group 3 subjects experienced a total of 4 TEAEs.

Table 6. Summary of Treatment Emergent Adverse Events – Safety Analysis Set

	Etanercept n=18	Placebo n=16	Total n=34
Number (%) of subjects with at least 1 TEAE	9 (50.0%)	3 (18.8%)	12 (35.3%)
Number of TEAEs	20	4	24
Number (%) of subjects with at least 1 TEAE related to study treatment	4 (22.2%)	1 (6.3%)	5 (14.7%)
Number of TEAEs related to study treatment	11	1	12
Number (%) of subject with at least 1 SAE	1 (5.6%)	-	1 (2.9%)
Number of SAEs	1	-	1
Number (%) of subjects with at least 1 SAE related to study treatment	1 (5.6%)	-	1 (2.9%)
Number of SAEs related to study treatment	1	-	1
Number (%) of subjects with at least 1 AE leading to study drug permanent discontinuation and/or study withdrawal	1 (5.6%)	1 (6.3%)	2 (5.9%)
Number of TEAEs leading to study drug permanent discontinuation and/or study withdrawal	1	1	2

AE/SAE results are not separated out.
AE = adverse event; n = number of subjects with specific events; SAE = serious adverse event; TEAE = treatment emergent adverse event.

In the etanercept group, the most frequent non serious TEAE was injection site erythema (3 subjects). Most TEAEs were of mild intensity. All non-serious TEAES by preferred terms are reported in Table 7.

Table 7. Non-Serious Treatment Emergent Adverse Events, by Preferred Term – Safety Analysis Set

MedDRA Preferred Term	Etanercept N=18		Placebo N=16	
	n (%) Subjects With at Least 1:	Number of AEs	n (%) Subjects With at Least 1:	Number of AEs
All	9 (50.0%)	19	3 (18.8%)	4
Injection site erythema	3 (16.7%)	9	-	-
Abdominal pain	1 (5.6%)	1	1 (6.3%)	1
Tooth abscess	2 (11.1%)	2	-	-
Urinary tract infection	1 (5.6%)	1	1 (6.3%)	1
Back pain	1 (5.6%)	1	-	-
Bronchitis	1 (5.6%)	1	-	-
Febrile infection	1 (5.6%)	1	-	-
Musculoskeletal chest pain	1 (5.6%)	1	-	-
Oropharyngeal pain	-	-	1 (6.3%)	1
Rash erythematous	1 (5.6%)	1	-	-
Rash papular	1 (5.6%)	1	-	-
Toothache	-	-	1 (6.3%)	1

Includes all data collected since the first injection of study drug to 15 days after the last injection. MedDRA (v 14.0) coding was applied.
AE = adverse event; MedDRA; Medical Dictionary for Regulatory Activities; N = total number of subjects, n = number of subjects with AE.

A total of 3 subjects experienced a total of 10 non serious TEAEs considered related to etanercept: injection site erythema (3 subjects) and rash erythematous. For 1 subject (6%), 1 AE was considered related to placebo: urinary tract infection which was of mild intensity and led to permanent treatment discontinuation and to study withdrawal.

One subject experienced a serious adverse event (SAE) of renal mass considered related to etanercept treatment and leading to study withdrawal.

In the etanercept group, treatment of 6 subjects was temporarily discontinued due to TEAEs (tooth abscess, urinary tract infection, rash erythematous, bronchitis, injection site erythema and febrile infection).

No deaths were reported during the study.

Median values for blood chemistry and hematology remained stable during the study and no clinically significant abnormality was reported by the investigators. No clinically significant abnormalities were reported in the urinalysis.

For 1 subject, total bilirubin was normal at baseline but potentially clinically important values were observed on-therapy (27.4 µmol/L at Week 12 and 25.8 µmol/L at Week 36).

Vital signs and physical examinations performed during the study did not show any changes.

CONCLUSIONS:

This study was prematurely terminated and results were available for only a small number of subjects with AS. In this population, there was an increase in FMD between baseline and week 12 in the etanercept group, but no statistically significant difference with the placebo group was shown. IMT was not significantly modified. Both ESR and CRP decreased in the etanercept group. All scores for assessment of AS activity showed an improvement in the etanercept group compared to placebo group. Etanercept was well tolerated in this population.