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

PROTOCOL NO.: 0881A3-404 (B1801006)

PROTOCOL TITLE: A Multicentre, Double-Blind, Placebo-Controlled, Randomized Study of Etanercept in the Treatment of Adults Patients With Refractory Heel Enthesitis in Spondylarthropathy

Study Centers: A total of 20 centers took part in the study of which 13 centers enrolled subjects; 10 in France, 2 in Germany and 1 in the Netherlands.

Study Initiation Date and Final Completion Date: January 2007 to September 2008

Phase of Development: Phase 4

Study Objectives:

Primary Objective: To compare the efficacy of etanercept (50 mg, once weekly) with that of placebo in subjects with refractory heel enthesitis in spondylarthropathy (SpA) at Week 12.

Secondary Objectives: To determine:

- The efficacy of etanercept compared with that of placebo at Weeks 2, 4, and 8;
- The impact of etanercept on heel enthesitis as evaluate by magnetic resonance imaging (MRI) compared with that of placebo at Week 12;
- The safety of etanercept in this subject population by analyzing safety data for all subjects receiving at least 1 dose of test article.

METHODS:

Study Design: This multicenter double-blind, placebo-controlled, randomized study evaluated the efficacy of etanercept for the treatment of refractory heel enthesitis in SpA. Eligible subjects were randomly assigned to receive either etanercept 50 mg or placebo, subcutaneously (SC), once weekly. Evaluations were performed as outlined: at Screening, Baseline, and at Weeks 2, 4, 8, and 12. The use of placebo as a control was necessary to allow a valid comparison and to provide a quantitative assessment of effect. A follow-up telephone call was required approximately 15 days after completing study treatment and in case of premature withdrawal from the study to assess for adverse events (AEs). The total duration of the study was 80 weeks: 20 weeks subject participation and up to 60 weeks enrollment. The schedule of activities for the study is presented in Table 1.

Table 1. Schedule of Activities

Study Procedures		Double-Blind, Placebo-Controlled Visit Windows			
	Screening[a]	Baseline Week 0	Weeks 2, 4, 8[b], ±3 days	Week 12 or Early Discontinuation Visit[b], ±3 days	Follow-Up Visit[c]
Signed informed consent	X				
Medical history	X	X			
Inclusion/exclusion	X	X			
Record prior/concomitant medications	X	X	X	X	
Adverse events	X	X	X	X	X
General physical examination	X	X	X	X	
Characteristic of the heel enthesitis	X	X	X	X	
Vital signs	X	X	X	X	
Chest x –ray film[d]	X				
Heel pain (VAS)	X	X	X	X	
Patient global assessment (VAS)	X	X	X	X	
BASDAI		X	X	X	
WOMAC function		X	X	X	
MCII/PASS			X	X	
The enthesitis index		X	X	X	
MRI[e]	X			X	
HLA B27[f]		X			
Serum or urinary pregnancy test[g]	X	X			
Chemistry/haematology/urinalysis	X	X	X	X	
Dispense test article		X	X[h]		
Dispense diary card		X	X[i]		

BASDAI = Bath Ankylosing Spondylitis Disease Activities Index; HLA B27 = Human Leukocyte Antigen B27; MCII = minimum clinically important improvement; MRI = magnetic resonance imaging; PASS = patient acceptable symptom state; VAS = visual analogue scale; WOMAC = Western Ontario and Mcmaster Universities Osteoarthritis Index.

a. Not more than 6 weeks before the baseline visit.
b. Visits could be scheduled up to 3 days before or after prescheduled visit.
c. Evaluations performed to follow-up on adverse events, approximately 15 days after last dose.
d. Chest X-ray film within 1 month of prestudy screening.
e. MRI performed within 3 months of prestudy screening was acceptable if realized according to the procedures and as per Investigator's discretion (images should be recorded on CD).
f. Waived if results were known and copy of laboratory report was in source documents.
g. If woman of childbearing potential. A serum pregnancy test was performed at Screening and a urinary pregnancy test was performed at Baseline. If any urinary pregnancy test was positive, a serum pregnancy test was performed.
h. Needed only at Week 2.
i. Needed at Weeks 4 and 8.

Number of Subjects (Planned and Analyzed): A total of 20 subjects, 10 in the etanercept group and 10 in the placebo group were planned for enrollment into the study. Twenty-four subjects were randomly assigned to receive test article; 12 subjects in the etanercept group and 12 in the placebo group.

Of the 24 subjects; 18 were enrolled in France, 4 in Germany, and 2 in the Netherlands.

Diagnosis and Main Criteria for Inclusion: Both male and female subjects aged between 18 years and 70 years, inclusive, who were diagnosed with SpA with heel enthesitis (refractory to standard treatment), were included in the study. The patient global assessment (PGA) of disease activity in the last 48 hours (100 mm visual analogue scale [VAS]) had to be >40 mm. All women of childbearing potential had to have a negative serum β-human chorionic gonadotropin pregnancy test at Screening. Sexually active men and women had to use a reliable form of contraception during the study. Subjects who had >1 local steroid injection within 2 weeks of screening, subjects with prior exposure to any tumor necrosis factor (TNF)-inhibitor (including etanercept), and subjects who had a dose of nonsteroidal anti-inflammatory drugs that changed within 2 weeks of study drug evaluation were excluded from the study.

Study Treatment: Etanercept (50 mg) and its matching placebo were supplied by the Sponsor in vials as sterile lyophilized powder. The diluent for rehydration of etanercept/placebo was sterile water for injection provided in a pre-filled syringes.

Test article SC injections were administered at approximately the same time of the day (±4 hours) and on the same day of the week. Each dose of test article was administered as 1 SC injection not consecutively in the same location; instead, additional administration sites (arms, thighs, abdomen, left/right) were used alternately for each consecutive dosing.

Efficacy Endpoints:

Primary Endpoint: The normalized net incremental area under the curve (AUC) between randomization and Week 12 for the PGA of disease activity. The PGA was measured by the 100 mm VAS.

Secondary Endpoints:

- The response at Week 12 defined as at least 50% improvement (decrease) from Baseline in the PGA of disease activity; this was measured by the 100 mm VAS;
- The improvement of the enthesitis between Baseline and Week 12, evaluated by MRI;
- The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function at Weeks 2, 4, 8, and 12;
- Global heel pain, measured by 100 mm VAS at Weeks 2, 4, 8 and 12;
- The Bath Ankylosing Spondylitis Disease Activities Index (BASDAI) at Baseline, Weeks 2, 4, 8, and 12;
- The Minimum Clinically Important Improvement (MCII) and the Patient Acceptable Symptom State (PASS) at Weeks 2, 4, 8 and 12;
- The enthesitis index at Baseline, Weeks 2, 4, 8, and 12.

Safety Evaluations: Safety evaluations included monitoring of AEs, withdrawal due to AEs, clinical laboratory evaluations, and findings in vital signs and physical examination.

Statistical Methods:

Analysis Populations:

Efficacy Populations: The population of primary interest was the modified intent-to-treat (mITT) population that included all randomized subjects who received at least 1 dose of blinded test article. In addition, analysis was also performed for the ITT population that included all randomized subjects.

Safety Population: The population of interest for safety analyses was the mITT population.

Additional Subgroup: Analysis population of MRI Criteria: 1 of the main inclusion criteria was the presence of bone edema in the calcaneum adjacent to the insertion site of either Achilleus tendon or fascia plantaris. Localization of edema was evaluated at Screening by Investigators and, then, evaluated by a centralized reading. All subjects included in the study had an edema according to Investigator's assessment while 5 subjects did not have edema according to the centralized reading. An additional analysis population for all MRI criteria was defined as "subjects with at least 1 edema (Achilleus tendon and/or fascia plantaris) at Screening according to centralized reading."

Statistical Methods: The normalized net incremental AUC between randomization and Week 12 was computed and analyzed using an analysis of covariance (ANCOVA) with treatment as a factor and baseline values as a covariate.

The absolute changes from Baseline to Week 12 was computed and analyzed using a mixed model ANCOVA and an autoregressive correlation structure, with treatment groups, visits and their interaction as fixed factors, subjects as a random factor, and baseline value as a covariate.

For binary efficacy criteria, a generalized estimating equations (GEE) model was used, with a logit link, a binomial distribution, and an auto-regressive correlation structure with treatment groups, visits and their interaction as fixed factors.

For multinomial secondary efficacy criteria, each of the 2 questions of the MCII were analyzed using a GEE model, a cumulative logit link, a multinomial distribution, and an autoregressive correlation structure; treatment groups and visits were used as fixed factors.

For improvement of the enthesitis between Baseline and Week 12, as evaluated by MRI, each continuous absolute variation from Baseline to Week 12, treatment groups was compared using an ANCOVA model adjusted on the baseline value.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is presented in Table 2. A total of 33 subjects were screened but 9 subjects were not randomized due to

either a lack of bone edema (according to the Investigator MRI reading, 8 subjects) or a withdrawal of consent (1 subject). Twenty-four subjects were randomly assigned to receive treatment. Five (20.8%) subjects discontinued the study after randomization (1 in the etanercept group and 4 in the placebo group).

Table 2. Subject Disposition

	Etanercept 50 mg/Week	Placebo	Total
Total	12 (50%)	12 (50%)	24 (100%)
Completed	11 (45.8%)	8 (33.3%)	19 (79.2%)
Discontinued	1 (4.2%)	4 (16.7%)	5 (20.8%)
Adverse event	1 (4.2%)	0 (0.0%)	1 (4.2%)
Investigator request: lack of compliance	0 (0.0%)	1 (4.2%)	1 (4.2%)
Investigator request: lack of efficacy	0 (0.0%)	3 (12.5%)	3 (12.5%)

The ITT population included 24 subjects; 12 in the etanercept group and 12 in the placebo group. All randomized subjects were treated. All subjects included in ITT population were included in the mITT population. Data from all 24 subjects who received at least 1 dose of study drug were included in the safety analyses.

A subgroup of 19 subjects (10 in the etanercept group and 9 in the placebo group) was identified by MRI criteria as having at least 1 edema in the calcaneum adjacent to the insertion site of either the Achilles tendons or adjacent to the fascia plantaris (according to the centralized reading at Screening).

A summary of subject demographics and medical history is presented in Table 3.

The study population consisted of SpA subjects with refractory heel enthesitis aged 18.1 to 57.2 years, with a mean age (±SD) of 37.3 years (±11.5). The majority of subjects were male (67%). All subjects (24, 100%) had at least 1 medical history related to SpA. Fifteen (62.5%) subjects had an axial involvement and 16 (66.7%) subjects had a peripheral arthritis.

Table 3. Summary of Demographic Characteristics and Medical History

Characteristic	p-Value[a]	50 mg/Week Etanercept N=12	Placebo N=12	Total N=24
Age, years				
N		12	12	24
Mean (±SD)	0.252	34.5 (±12.4)	40.0 (±10.4)	37.3 (±11.5)
Median		32.1	41.5	38.9
Minimum-Maximum		(18.6; 53.7)	(18.1; 57.2)	(18.1; 57.2)
Gender, n (%)				
Female	0.667	5 (41.67%)	3 (25.00%)	8 (33.33%)
Male		7 (58.33%)	9 (75.00%)	16 (66.67%)
Medical history related to spondylarthropathy (SpA)	1.000	12 (100.00%)	12 (100.00%)	24 (100.00%)
Cutaneous psoriasis	1.000	2 (16.67%)	2 (16.67%)	4 (16.67%)
Ungueal psoriasis	1.000	1 (8.33%)	2 (16.67%)	3 (12.50%)
Crohn's disease	NA	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis	NA	0 (0.00%)	0 (0.00%)	0 (0.00%)
Uveitis	0.478	2 (16.67%)	0 (0.00%)	2 (8.33%)
Axial involvement	1.000	8 (66.67%)	7 (58.33%)	15 (62.50%)
Peripheral arthritis	1.000	8 (66.67%)	8 (66.67%)	16 (66.67%)
Urethritis, colpitis/cervicitis	1.000	2 (16.67%)	1 (8.33%)	3 (12.50%)
Reiter's syndrome	NA	0 (0.00%)	0 (0.00%)	0 (0.00%)
'Sausage-like' finger or toe	0.680	4 (33.33%)	6 (50.00%)	10 (41.67%)
Other medical history related to SpA[b]	0.217	3 (25.00%)	0 (0.00%)	3 (12.50%)

N = number of subjects; n = number of subjects with specified criteria; SD = standard deviation; SpA = spondylarthropathy.
a. Analysis of variance (ANOVA) for continuous criteria, Fisher exact test for qualitative criteria.
b. One subject had low back pain (stable), 1 subject had reactive arthritis after enteritis (resolved), and 1 subject had right knee enthesopathy (stable).

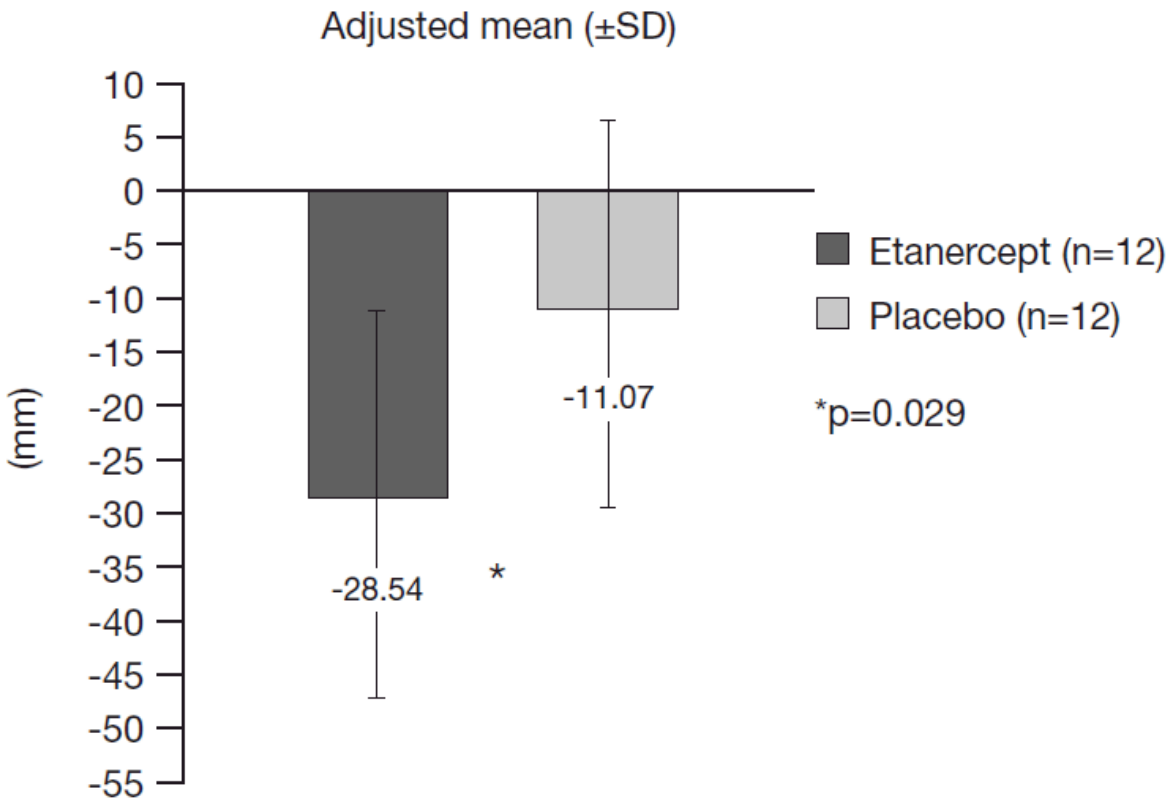
Efficacy Results:

Primary Endpoint

Normalized Net Incremental AUC Between Randomization and Week 12 for the PGA of Disease Activity:

The PGA decrease observed from Baseline to Week 12 was statistically higher in the etanercept group in comparison to the placebo group (adjusted means: -28.54 mm; 95% Confidence Interval [CI]=[-39.35 mm; -17.72 mm] versus -11.07 mm; 95% CI=[-21.88 mm; -0.25 mm]; p-value=0.029). Results of the normalized net incremental AUC of patient global assessment are summarized in Figure 1.

Figure 1. Normalized Net Incremental AUC of Patient Global Assessment



AUC = area under the curve; n = number of subjects in each group; SD = standard deviation.

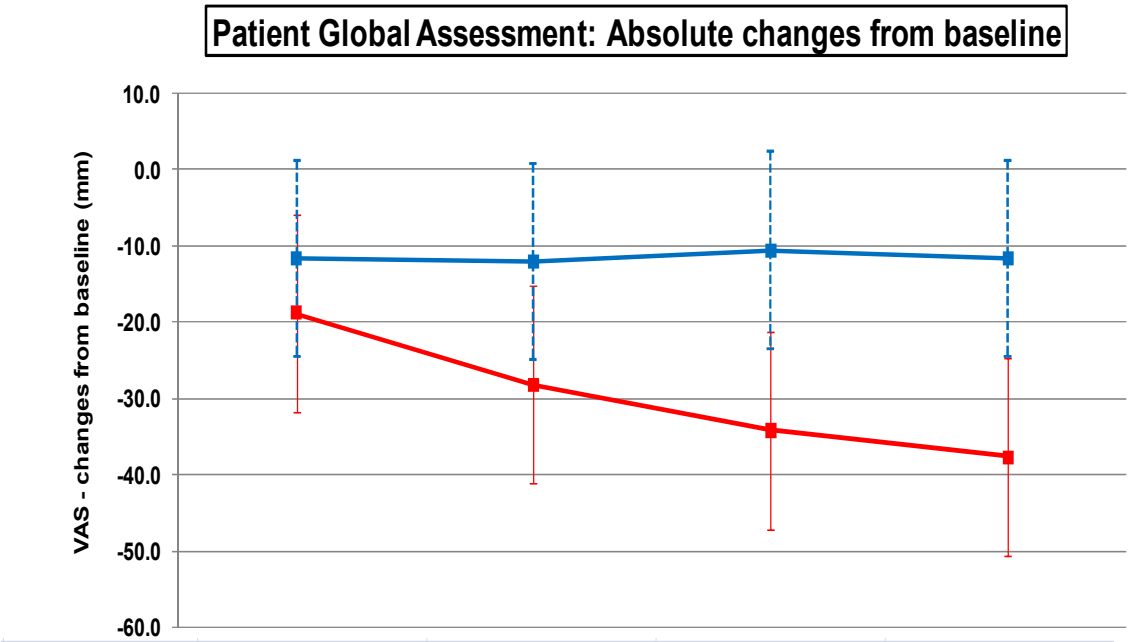
Secondary Endpoints

Response at Week 12 From Baseline in thePGA of Disease Activity:

The absolute change from Baseline to Week 12 on the PGA of disease activity was statistically higher (p-value=0.007) in the etanercept group (adjusted means: -37.59 mm; 95% CI=[-50.50 mm; -24.67 mm]) than in the placebo group (-11.58 mm; 95% CI=[-24.50 mm; 1.33 mm]). The absolute change from Baseline to Week 8 was also statistically higher (p-value=0.013) in etanercept group (adjusted means: -34.15 mm; 95% CI=[-47.07 mm; -21.24 mm]) than in placebo group (-10.53 mm; 95% CI=[-23.45 mm; 2.38 mm]). No statistically significant difference between treatment groups was observed before Week 8.

Mean PGA changes from Baseline are summarized in Figure 2.

Figure 2. Absolute Change From Baseline of Patient Global Assessment



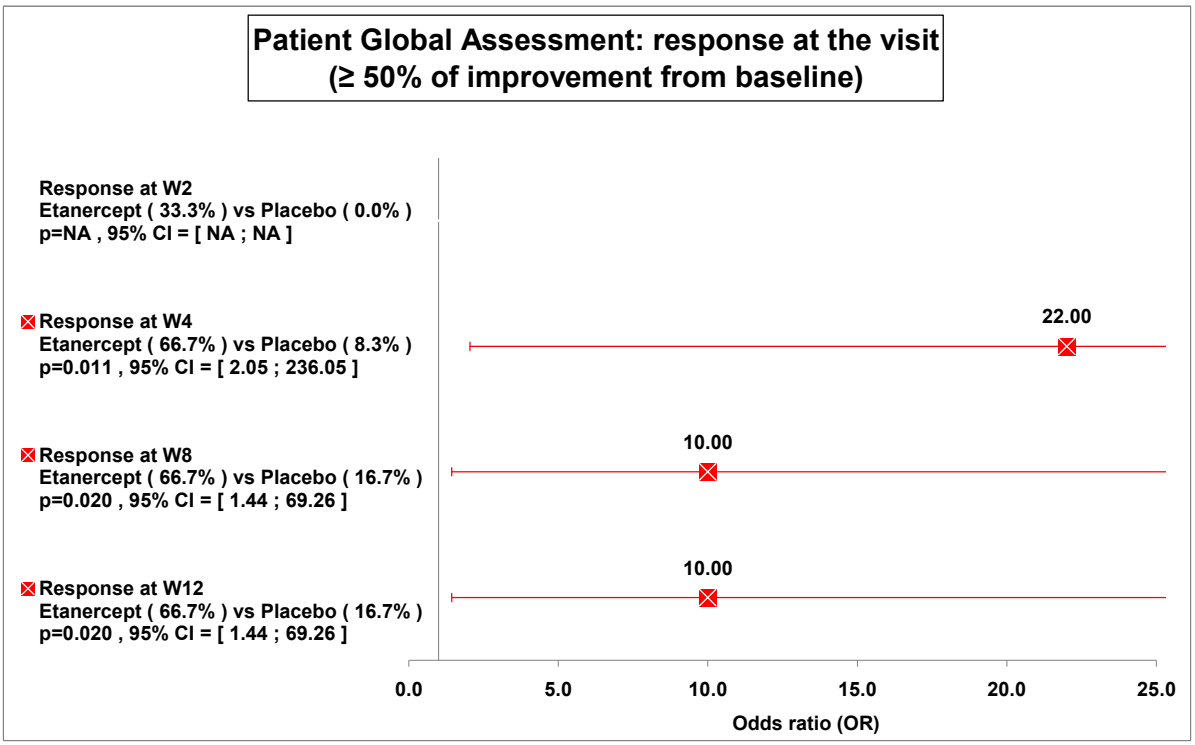
Adjusted mean [95%CI]	W2-baseline	W4-baseline	W8-baseline	W12-baseline
Etanercept (N=12)	-18.79 [-31.70;-5.87]	-28.14 [-41.05;-15.22]	-34.15 [-47.07;-21.24]	-37.59 [-50.50;-24.67]
Placebo (N=12)	-11.60 [-24.51;1.32]	-12.02 [-24.94;0.90]	-10.53 [-23.45;2.38]	-11.58 [-24.50;1.33]
p-value[a]	p=0.433	p=0.084	p=0.013	p=0.007

a: from a mixed model analysis of covariance (ANCOVA), using an auto-regressive correlation structure, with treatment groups, visits and their interaction as fixed factors, baseline value as a covariate and patients as a random factor.

CI = confidence interval; N = number of subjects in each group; W = week; VAS = visual analogue scale.

The 50% response rates at Weeks 8 and 12 were statistically higher in etanercept group than in placebo group (odds ratio [OR]=10.00; 95% CI=[1.44; 69.26]; p-value=0.020). The response rate at Week 4 was also statistically higher in etanercept group than in placebo group (OR=22.00; 95% CI=[2.05; 236.05]; p-value=0.011). At week 2, a response was observed for 4 (33.3%) subjects in the etanercept group whereas no response was observed in the placebo group. Since no response in the placebo group was observed at Week 2, this visit could not be analyzed in the GEE model. Results of the response rate at the visit of PGA are summarized in Figure 3.

Figure 3. Response Rate of the Patient Global Assessment



CI = confidence interval; NA = not applicable; vs = versus; W = week.

Improvement of the Enthesitis Between Baseline and Week 12, as Evaluated by MRI:

Heel enthesitis was evaluated through MRI at Screening and at Week 12 and presence of edema in the calcaneum (adjacent to the insertion of either Achilles tendon and/or fascia plantaris) was detected.

MRI Criteria: Achilles Tendon: Achilles Insertion Thickness (mm) and Achilles Tendon Edema Extension (mm):

The difference between both groups concerning the adjusted change from Baseline to Week 12 of Achilles insertion thickness was not statistically significant (p-value=0.982). The difference between both groups concerning the adjusted change from Baseline to Week 12 of Achilles tendon edema extension was not statistically significant. Results for insertion thickness and edema extension of the Achilleus tendon are summarized in Table 4.

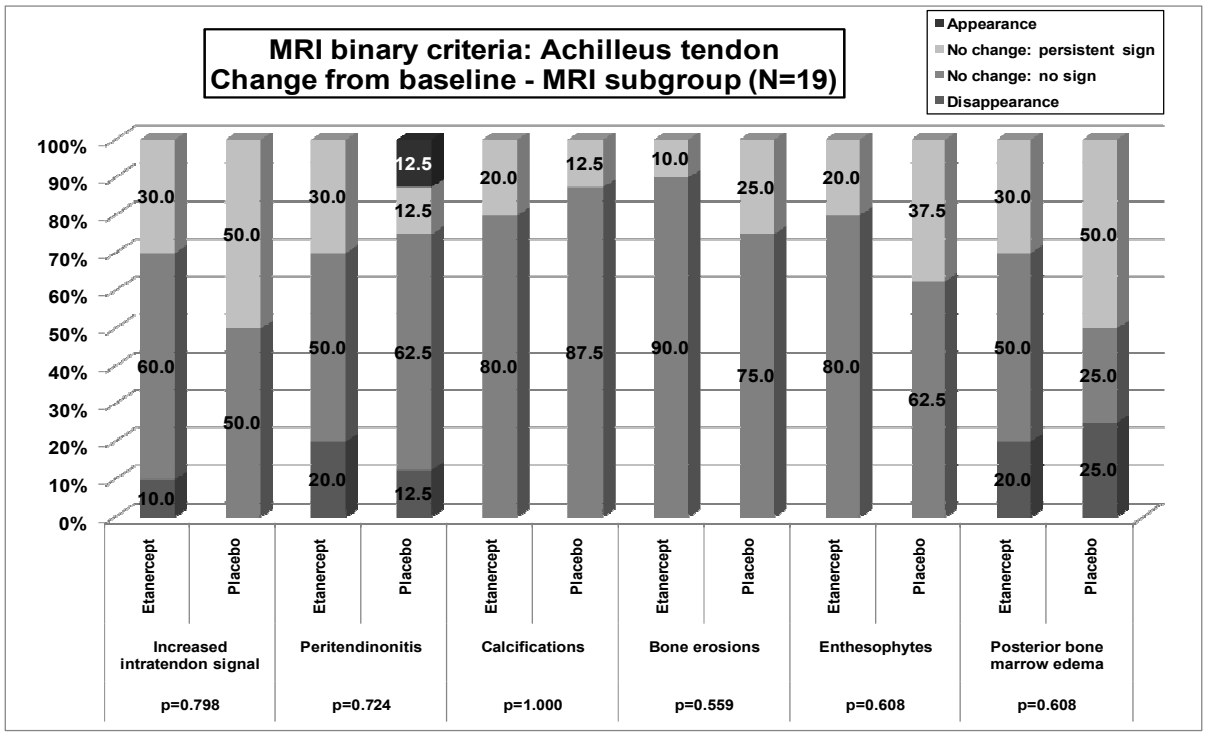
Table 4. MRI Criteria: Achilles Tendon: Change From Baseline on MRI Subgroup (N=19)

Characteristic	50 mg/Week Etanercept (N=10)	Placebo (N=9)	Difference	p-Value[a]
Achilles tendon				
Achilles insertion thickness, mm (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-0.11 (±0.79)	-0.11 (±0.79)	-0.01	0.982
95% CI	(-0.64; 0.41)	(-0.70; 0.49)	(-0.80; 0.79)	
Edema extension, mm (Week 12 – Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-1.41 (±10.06)	-3.86 (±10.11)	2.45	0.625
95% CI	(-8.19; 5.37)	(-11.48; 3.76)	(-7.99;12.89)	

ANCOVA = analysis of covariance; CI = confidence interval; MRI = magnetic resonance imaging; N = number of subjects; SD = standard deviation.
a. From an ANCOVA.
b. MRI criterion for one subject not evaluated at Week 12.

No statistically significant difference was observed between treatment groups concerning the change from Baseline to Week 12 of the following Achilles tendon criteria: increased intratendon signal, peritendononitis, calcifications, bone erosions, enthesophytes, and posterior bone marrow edema. The results are summarized in Figure 4.

Figure 4. MRI Binary Criteria: Achilleus Tendon: Change From Baseline on MRI

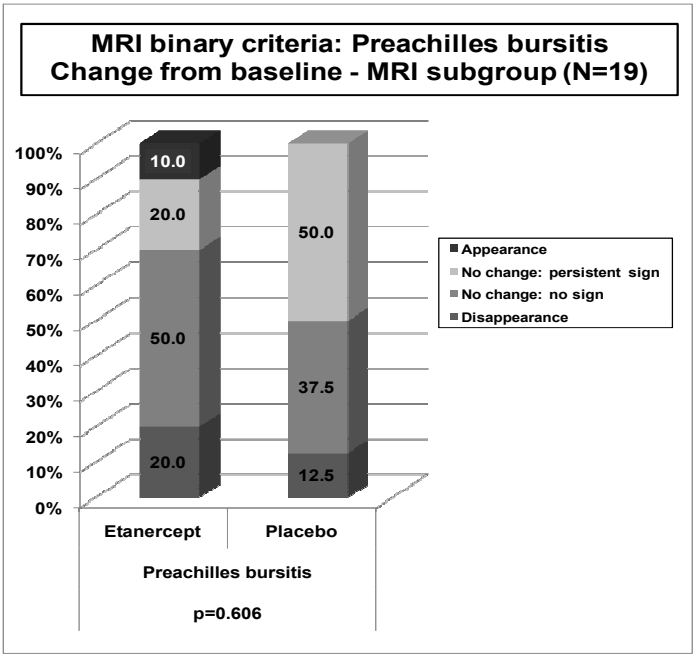


MRI = magnetic resonance imaging; N = number of evaluated subjects.

MRI Criteria: Pre-Achilles Bursitis:

No statistically significant difference was observed between treatments groups concerning the change from Baseline to Week 12 of pre-Achilles bursitis. The results are summarized in Figure 5.

Figure 5. MRI Binary Criteria: Preachilles Bursitis: Change From Baseline on MRI



MRI = magnetic resonance imaging; N = number of evaluated subjects.

MRI Criteria: Fascia Plantaris: Fascia Plantaris Thickness (mm) and Fascia Plantaris Edema Extension (mm):

The difference between both groups concerning the adjusted change from Baseline to Week 12 of fascia plantaris thickness and edema extension on fascia plantaris was not statistically significant. Results for thickness and edema extension on the fascia plantaris are summarized in Table 5.

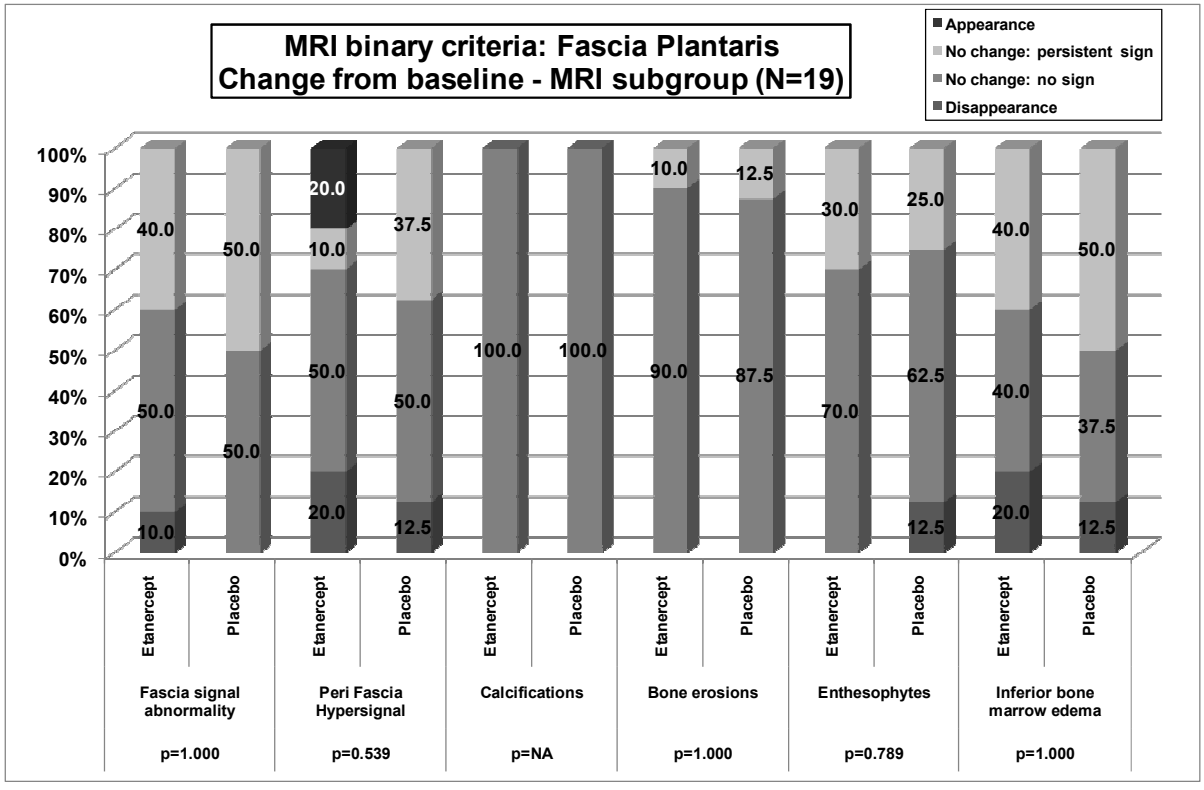
Table 5. MRI Criteria: Fascia Plantaris: Change From Baseline, on MRI Subgroup (N=19)

Characteristic	50 mg/Week Etanercept (N=10)	Placebo (N=9)	Difference	p-Value[a]
Fascia plantaris				
Thickness, mm (Week 12 – Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-0.30 (±1.08)	0.25 (±1.08)	-0.55	0.300
95% CI	(-1.03; 0.43)	(-0.56; 1.06)	(-1.64; 0.54)	
Edema extension, mm (Week 12 – Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-6.62 (±12.91)	-6.48 (±12.94)	-0.14	0.983
95% CI	(-15.32; 2.09)	(-16.23; 3.27)	(-13.34; 13.07)	

ANCOVA = analysis of covariance; CI = confidence interval; MRI = magnetic resonance imaging; N = number of subjects; SD = standard deviation.
a. From an ANCOVA.
b. MRI criterion for one subject not evaluated at Week 12.

No statistically significant difference was observed between treatment groups concerning the change from Baseline to Week 12 of the following fascia plantaris criteria: fascia signal abnormality, perifascia hypersignal, calcifications, bone erosions, enthesophytes, and inferior bone marrow edema. The results are summarized in Figure 6.

Figure 6. MRI Binary Criteria: Fascia Plantaris: Change From Baseline on MRI



MRI = magnetic resonance imaging; N = number of evaluated subjects.

Additional MRI Scores:

Whatever the MRI scoring system (ie, with or without taking into account the level of the edema [in Achilles tendon and in fascia plantaris]) using a weighted scoring, with or without taking into account all abnormalities of both Achilles tendon and fascia plantaris, no statistically significant difference was observed between treatment groups in absolute changes scores from Baseline to Week 12. Nevertheless, in regards to standardized response mean observed in both treatment groups, all the MRI scoring systems were able to accurately detect changes in heel enthesitis. The scoring systems taking into account both the calcaneum edema and the tendon/fascia abnormalities (ie, the 7- and 13-grade scales) seemed to be the most discriminant.

Table 6. Additional MRI Scores of Heel Enthesitis: Change From Baseline

Characteristic	50 mg/Week Etanercept (N=10)	Placebo N=9	Difference	p-Value[a]
MRI Scores Computed Without Quartiles Weighting				
MRI score range 0-7 (Week 12 – Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-1.00 (±1.36)	-0.50 (±1.36)	-0.50	0.457
95% CI	(-1.92; -0.08)	(-1.53; 0.53)	(-1.89; 0.89)	
SRM	-0.73	-0.37		
MRI score range 0-5 (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-0.54 (±0.93)	-0.20 (±0.93)	-0.35	0.446
95% CI	(-1.17; 0.08)	(-0.90; 0.51)	(-1.29; 0.60)	
SRM	-0.58	-0.21		
MRI score range 0-2 (Week 12 - Baseline)				
-2	1 (10.00%)	1 (12.50%)	NA	
-1	2 (20.00%)	1 (12.50%)	NA	
0	7 (70.00%)	6 (75.00%)	NA	NA
1	0 (0.00%)	0 (0.00%)	NA	
2	0 (0.00%)	0 (0.00%)	NA	
MRI score range 0-3 (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-0.70 (±1.00)	-0.38 (±1.00)	-0.33	p=0.505
95% CI	(-1.38; -0.02)	(-1.13; 0.38)	(-1.34; 0.69)	
SRM	-0.70	-0.37		
MRI Scores Computed With Quartiles Weighting				
MRI score range 0-13 (Week 12 - Baseline)				
N	10	9		
Adjusted mean (±SD)	-1.89 (±2.67)	-1.23 (±2.67)	-0.66	p=0.597
95% CI	(-3.68; -0.11)	(-3.11; 0.65)	(-3.27; 1.94)	
SRM	-0.71	-0.46		
MRI score range 0-8 (Week 12 - Baseline)				
N	10	9		
Adjusted mean (±SD)	-1.39 (±2.01)	-0.90 (±2.01)	-0.49	0.606
95% CI	(-2.74; -0.04)	(-2.32; 0.52)	(-2.46; 1.48)	
SRM	-0.69	-0.45		
MRI score range 0-6 (Week 12 - Baseline)				
N	10	9		
Adjusted mean (±SD)	-1.40 (±2.07)	-0.78 (±2.07)	-0.61	0.530
95% CI	(-2.78; -0.01)	(-2.25; 0.68)	(-2.64; 1.41)	
SRM	-0.67	-0.38		
Edema Extensions, mm				
Edema extension (target edema based on pain location), mm (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-6.96 (±16.25)	-5.56 (±16.26)	-1.40	0.859
95% CI	(-17.91; 4.00)	(-17.81; 6.70)	(-17.88; 15.08)	
SRM	-0.43	-0.34		
Edema extension (target edema based on maximum edema at screening), mm (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-6.96 (±16.25)	-5.56 (±16.26)	-1.40	0.859
95% CI	(-17.91; 4.00)	(-17.81; 6.70)	(-17.88; 15.08)	
SRM	-0.43	-0.34		
Sum of edema extensions (achilleus tendon + fascia plantaris), mm (Week 12 - Baseline)				
N	10	8[b]		
Adjusted mean (±SD)	-10.60 (±16.44)	-7.12 (±16.44)	-3.48	0.662
95% CI	(-21.68; 0.48)	(-19.51; 5.27)	(-20.11; 13.15)	
SRM	-0.64	-0.43		

Table 6. Additional MRI Scores of Heel Enthesitis: Change From Baseline

ANCOVA = analysis of covariance; CI = confidence interval; MRI = magnetic resonance imaging; N = number of subjects; SD = standard deviation; SRM = standardized response mean.
a. From an ANCOVA.
b. MRI criterion for 1 subject not evaluated at Week 12.

WOMAC Index Function at Weeks 2, 4, 8 and 12:

There was no significant difference between etanercept and placebo groups regarding the normalized net incremental AUC of the WOMAC function.

No statistically significant difference between treatment groups was observed in the changes from baseline to Weeks 2, 4 and 8. Nevertheless, the change from baseline to Week 12 was statistically higher in the etanercept group than in the placebo group (p-value=0.024). Results of WOMAC Index function are summarized in Table 7.

Table 7. WOMAC Index Function

Characteristic	50 mg/Week Etanercept (N=12)	Placebo (N=12)	Difference	p-Value[a]
Normalized Net Incremental AUC, mm				
Adjusted mean (±SD)	-17.98 (±14.08)	-7.88 (±14.08)	-10.09	0.096
95% CI	(-26.43; -9.52)	(-16.33; 0.57)	(-22.14; 1.96)	
Absolute Changes From Baseline, mm				
Week 2 - Baseline				
Adjusted mean (±SD)	-14.63 (±15.98)	-9.02 (±15.98)	-5.61	0.398
95% CI	(-23.96; -5.31)	(-18.35; 0.30)	(-18.88; 7.65)	
Week 4 - Baseline				
Adjusted mean (±SD)	-18.23 (±15.98)	-6.14 (±15.98)	-12.10	0.073
95% CI	(-27.56; -8.91)	(-15.46; 3.19)	(-25.36; 1.17)	
Week 8 - Baseline				
Adjusted mean (±SD)	-20.50 (±15.98)	-9.62 (±15.98)	-10.88	0.105
95% CI	(-29.82; -11.17)	(-18.94; -0.29)	(-24.15; 2.39)	
Week 12 - Baseline				
Adjusted mean (±SD)	-23.19 (±15.98)	-7.78 (±15.98)	-15.41	0.024
95% CI	(-32.52; -13.87)	(-17.11; 1.54)	(-28.67; -2.14)	

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; N = number of subjects; SD = standard deviation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index.
a. From a mixed model ANCOVA.

The Global Heel Pain at Each Visit:

The heel pain decrease evaluated using the normalized net incremental AUC was statistically higher in the etanercept group than in the placebo group (p-value=0.018).

The absolute heel pain changes from Baseline to Weeks 2 and 4 were borderline, not statistically significant between groups. From 8 weeks of treatment, the difference became statistically significant in favor of the etanercept group (p-value=0.013). This difference was sustained until 12 weeks of treatment (p-value=0.022). Results of heel pain are summarized in Table 8.

Table 8. Global Heel Pain

Characteristic	50 mg/Week Etanercept (N=12)	Placebo (N=12)	Difference	p-Value[a]
Normalized Net Incremental AUC, mm				
Adjusted mean (±SD)	-30.21 (±19.68)	-9.44 (±19.68)	-20.76	0.018
95% CI	(-42.02; -18.39)	(-21.26; 2.37)	(-37.64; -3.88)	
Absolute Changes From Baseline, mm				
Week 2 - Baseline				
Adjusted mean (±SD)	-24.49 (±24.04)	-5.89 (±24.04)	-18.60	0.067
95% CI	(-38.50; -10.48)	(-19.90; 8.12)	(-38.56; 1.36)	
Week 4 - Baseline				
Adjusted mean (±SD)	-28.20 (±24.04)	-10.24 (±24.04)	-17.96	0.076
95% CI	(-42.21; -14.19)	(-24.25; 3.77)	(-37.92; 2.00)	
Week 8 - Baseline				
Adjusted mean (±SD)	-36.08 (±24.04)	-10.50 (±24.04)	-25.58	0.013
95% CI	(-50.10; -22.07)	(-24.51; 3.51)	(-45.54; -5.62)	
Week 12 - Baseline				
Adjusted mean (±SD)	-36.67 (±24.04)	-13.07 (±24.04)	-23.60	0.022
95% CI	(-50.68; -22.66)	(-27.08; 0.95)	(-43.56; -3.65)	

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; N = number of subjects; SD = standard deviation.
a. From a mixed model ANCOVA

BASDAI at Baseline, Weeks 2, 4, 8, and 12:

There was no statistically significant difference between both groups concerning the normalized net incremental AUC of the BASDAI.

No statistically significant difference between treatment groups was observed concerning absolute changes from Baseline to each visit: Weeks 2, 4, 8 and 12. The higher adjusted difference was observed at Week 12 in favor of the etanercept group (p-value=0.090). Results of the BASDAI are summarized in Table 9.

Table 9. BASDAI Results

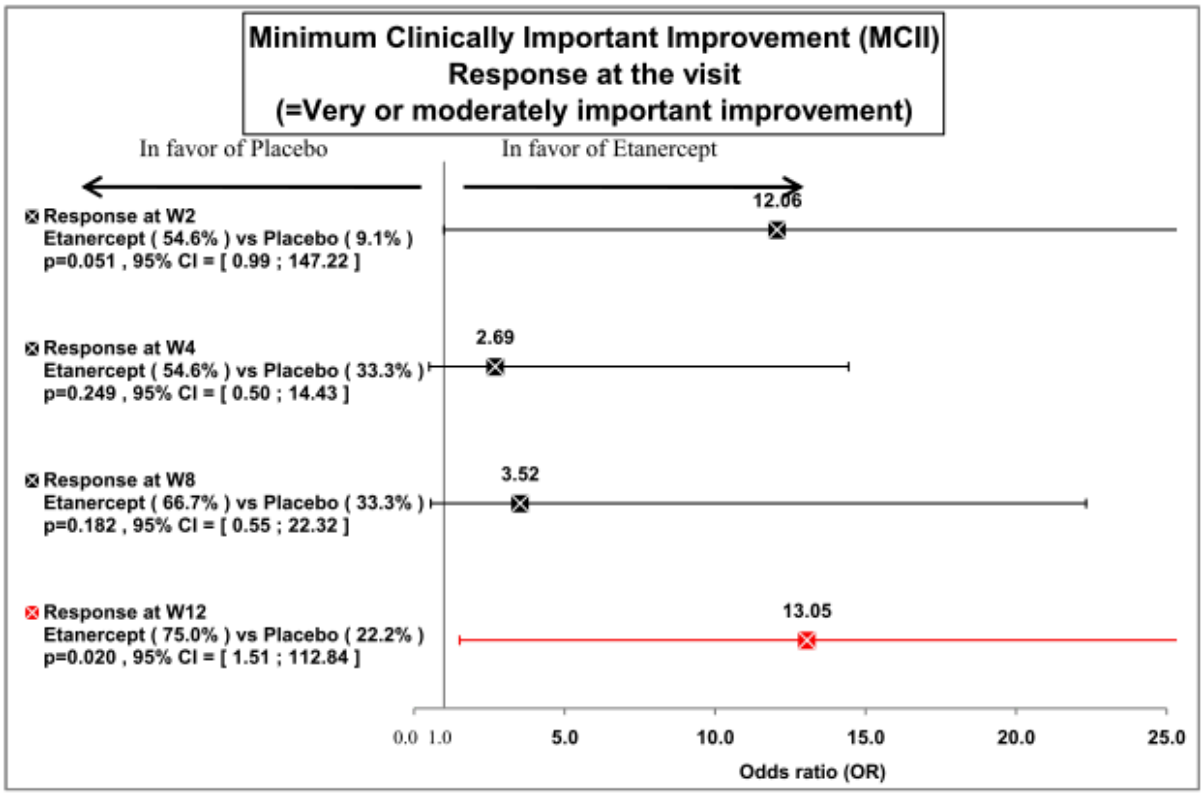
Characteristic	50 mg/Week Etanercept (N=12)	Placebo (N=11[b])	Difference	p-Value[a]
Normalized Net Incremental AUC, mm				
Adjusted mean (±SD)	-14.47 (±17.81)	-6.94 (±17.82)	-7.53	0.327
95% CI	(-25.19; -3.75)	(-18.15; 4.27)	(-23.18; 8.12)	
Absolute Changes From Baseline, mm				
Week 2 - Baseline				
Adjusted mean (±SD)	-24.49 (±24.04)	-5.89 (±24.04)	-18.60	0.067
95% CI	(-38.50; -10.48)	(-19.90; 8.12)	(-38.56; 1.36)	
Week 4 - Baseline				
Adjusted mean (±SD)	-28.20 (±24.04)	-10.24 (±24.04)	-17.96	0.076
95% CI	(-42.21; -14.19)	(-24.25; 3.77)	(-37.92; 2.00)	
Week 8 - Baseline				
Adjusted mean (±SD)	-36.08 (±24.04)	-10.50 (±24.04)	-25.58	0.013
95% CI	(-50.10; -22.07)	(-24.51; 3.51)	(-45.54; -5.62)	
Week 12 - Baseline				
Adjusted mean (±SD)	-36.67 (±24.04)	-13.07 (±24.04)	-23.60	0.022
95% CI	(-50.68; -22.66)	(-27.08; 0.95)	(-43.56; -3.65)	

ANCOVA = analysis of covariance; AUC = area under the curve; BASDAI = Bath Ankylosing Spondylitis Disease Activities Index; CI = confidence interval; N = number of subjects; SD = standard deviation.
a. From a mixed model ANCOVA.
b. BASDAI for 1 subject not evaluated at Baseline.

MCII and PASS:

The response rate of the MCII rated by 'very or moderately important improvements' was statistically higher in etanercept group than in placebo group at Week 12 (etanercept [75.0%] versus placebo [22.2%], p-value=0.020, 95% CI=[1.51; 112.84]). No statistically significant difference between treatment groups was observed at Weeks 2, 4, and 8. Results of the MCII are summarized in Figure 7.

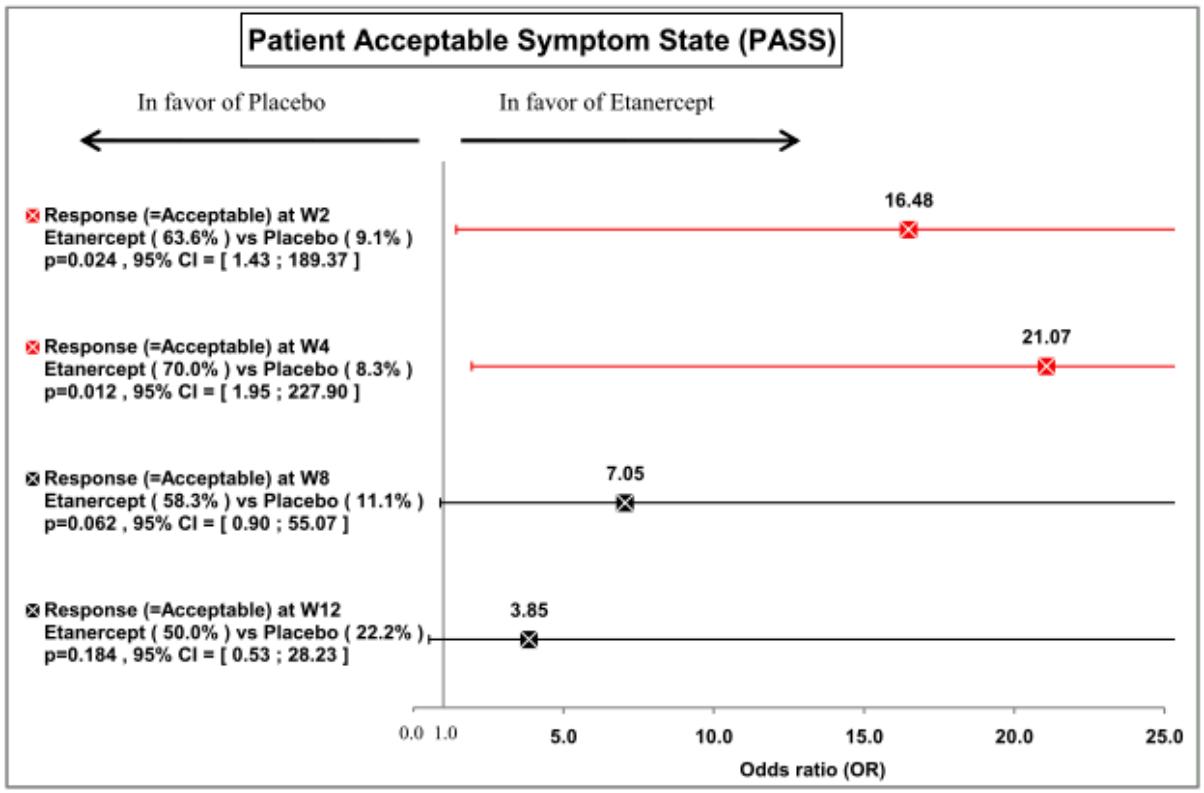
Figure 7. Minimum Clinically Important Improvement



CI = confidence interval; W = week; vs = versus.

The response rate 'acceptable' of the PASS questionnaire was statistically higher in the etanercept group than in the placebo group at Weeks 2 (p-value=0.024) and 4 (p-value=0.012). No statistically significant difference between treatment groups was observed at Weeks 8 and 12. Response for etanercept versus placebo at Week 2: 63.6% versus 9.1%, p-value=0.024, 95% CI=(1.43; 189.37); at Week 4: 70.0% versus 8.3%, p-value=0.012, 95% CI=(1.95; 227.90); at Week 8: 58.3% versus 11.1%, p-value=0.062, 95% CI=(0.90; 55.07); at Week 12: 50.0% versus 22.2%, p-value=0.184, 95% CI=(0.53; 28.23). Results for PASS are summarized in Figure 8.

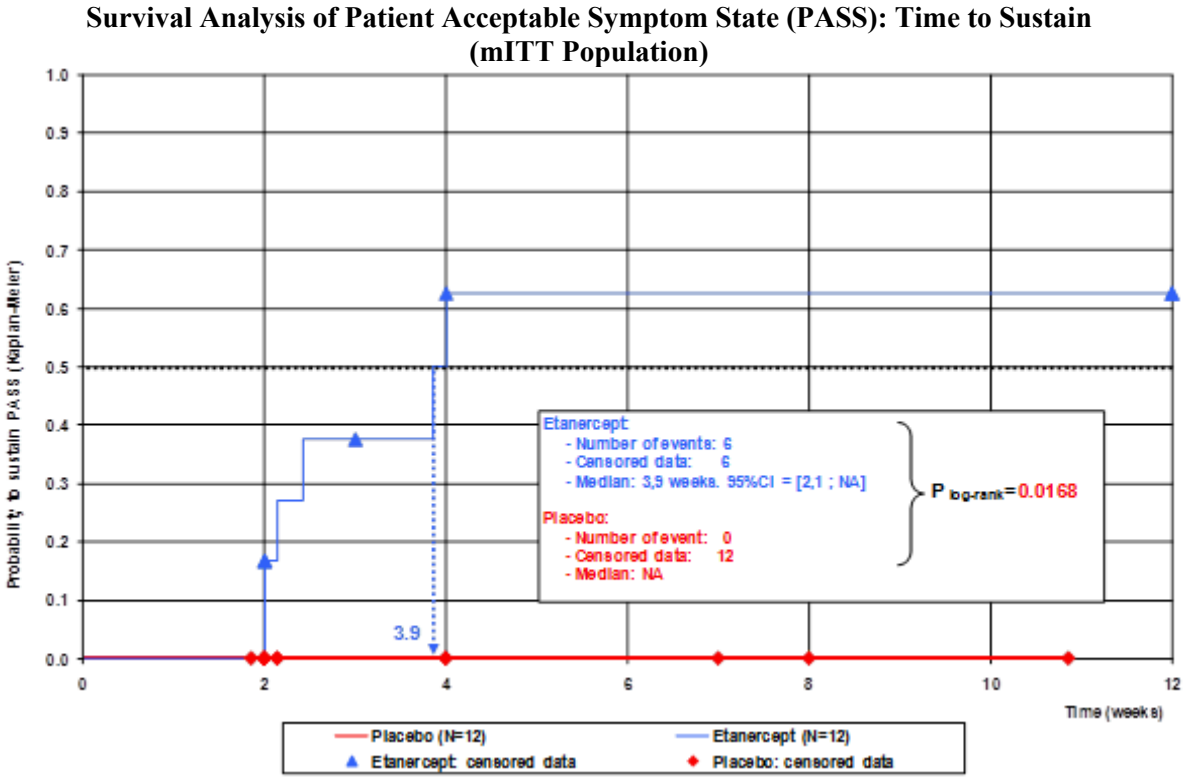
Figure 8. Patient Acceptable Symptom State



CI = confidence interval; W = week; vs = versus.

Six (50%) subjects in the etanercept group had an 'acceptable' symptom state sustained for at least 2 consecutive visits until Week 12 with a median sustainment time of 3.9 weeks (95% CI=[2,1; not estimated]) versus none in the placebo group. This difference was statistically significant (p-value=0.0168). Results of the time to achieve a sustained PASS are summarized in Figure 9.

Figure 9. Time to Achieve a Sustained Patient Acceptable Symptom State



CI = confidence interval; mITT = modified intent-to-treat; N = number of subjects in each group; NA = not applicable; PASS = patient acceptable symptom state; W = week; vs = versus.

Enthesitis Index at Baseline, Weeks 2, 4, 8 and 12:

Enthesitis index was assessed using the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Score. There was no statistically significant difference between both groups concerning the normalized net incremental AUC of the enthesitis index. There was no statistically significant difference between both groups concerning the changes from Baseline at the different visits. Results of the enthesitis index are summarized in Table 10.

Table 10. Enthesitis Index Using the MASES Score

Characteristic	50 mg/week Etanercept (N=12)	Placebo (N=12)	Difference	p-Value[a]
Normalized Net Incremental AUC, mm				
Adjusted mean (±SD)	-0.12 (±1.14)	-0.04 (±1.14)	-0.08	0.863
95% CI	(-0.81; 0.57)	(-0.72; 0.65)	(-1.05; 0.89)	
Absolute Changes From Baseline, mm				
Week 2 - Baseline				
Adjusted mean (±SD)	0.12 (±1.58)	0.13 (±1.58)	-0.02	0.977
95% CI	(-0.81; 1.04)	(-0.79; 1.06)	(-1.33; 1.29)	
Week 4 - Baseline				
Adjusted mean (±SD)	0.03 (±1.58)	-0.28 (±1.58)	0.31	0.629
95% CI	(-0.89; 0.96)	(-1.21; 0.64)	(-0.99; 1.62)	
Week 8 - Baseline				
Adjusted mean (±SD)	-0.22 (±1.58)	0.22 (±1.58)	-0.44	0.505
95% CI	(-1.14; 0.71)	(-0.71; 1.14)	(-1.74; 0.87)	
Week 12 - Baseline				
Adjusted mean (±SD)	-0.55 (±1.58)	0.13 (±1.58)	-0.69	0.296
95% CI	(-1.48; 0.37)	(-0.79; 1.06)	(-1.99; 0.62)	

ANCOVA = analysis of covariance; AUC = area under the curve; CI = confidence interval; MASES = Maastricht Ankylosing Spondylitis Enthesitis; N = number of subjects; SD = standard deviation.
a. From a mixed model ANCOVA.

Safety Results:

Treatment-Emergent AEs (TEAEs): Table 11 presents number of subjects, total of 22 (91.7%), with TEAEs reported during the study. The most common TEAEs reported in the etanercept group were injection site reaction and abdominal pain, each reported by 3 (25%) subjects, headache, and pharyngolaryngeal pain, each reported by 2 (17%) subjects. The most common TEAEs reported in the placebo group were nausea and asthenia, each reported by 2 (17%) subjects.

Table 11. Treatment-Emergent Adverse Events

System Organ Class Preferred Term	50 mg/Week Etanercept N=12 n (%)	Placebo N=12 n (%)	Total N=24 n (%)
Any adverse events	11 (91.7)	11 (91.7)	22 (91.7)
Cardiac disorders	1 (8.3)	-	1 (4.2)
Chest pain	1 (8.3)	-	1 (4.2)
Eye disorders	1 (8.3)	1 (8.3)	2 (8.3)
Uveitis	1 (8.3)	1 (8.3)	2 (8.3)
Gastrointestinal disorders	4 (33.3)	2 (16.7)	6 (25)
Abdominal pain	1 (8.3)	-	1 (4.2)
Abdominal pain upper	2 (16.7)	-	2 (8.3)
Dyspepsia	1 (8.3)	-	1 (4.2)
Nausea	-	2 (16.7)	2 (8.3)
General disorders and administration site conditions	5 (41.7)	3 (25)	8 (33.3)
Asthenia	1 (8.3)	2 (16.7)	3 (12.5)
Fatigue	1 (8.3)	-	1 (4.2)
Injection site hypersensitivity	1 (8.3)	-	1 (4.2)
Injection site pruritus	1 (8.3)	-	1 (4.2)
Injection site reaction	1 (8.3)	1 (8.3)	2 (8.3)
Malaise	-	1 (8.3)	1 (4.2)
Infections and infestations	5 (41.7)	3 (25)	8 (33.3)
Bronchitis	-	1 (8.3)	1 (4.2)
Cellulitis	1 (8.3)	-	1 (4.2)
Influenza	1 (8.3)	-	1 (4.2)
Nasopharyngitis	1 (8.3)	-	1 (4.2)
Pharyngitis	-	1 (8.3)	1 (4.2)
Rhinitis	1 (8.3)	1 (8.3)	2 (8.3)
Tracheitis	1 (8.3)	.	1 (4.2)
Injury, poisoning and procedural complications	1 (8.3)	1 (8.3)	2 (8.3)
Arthropod bite	-	1 (8.3)	1 (4.2)
Procedural headache	-	1 (8.3)	1 (4.2)
Traumatic haematoma	1 (8.3)	-	1 (4.2)
Investigations	-	2 (16.7)	2 (8.3)
Alanine aminotransferase increased	-	1 (8.3)	1 (4.2)
Transaminases increased	-	1 (8.3)	1 (4.2)
Musculoskeletal and connective tissue disorders	-	1 (8.3)	1 (4.2)
Arthralgia	-	1 (8.3)	1 (4.2)
Nervous system disorders	2 (16.7)	1 (8.3)	3 (12.5)
Headache	2 (16.7)	1 (8.3)	3 (12.5)
Psychiatric disorders	2 (16.7)	-	2 (8.3)
Anxiety	1 (8.3)	-	1 (4.2)
Restlessness	1 (8.3)	-	1 (4.2)
Renal and urinary disorders	1 (8.3)	1 (8.3)	2 (8.3)
Glycosuria	-	1 (8.3)	1 (4.2)
Haematuria	1 (8.3)	-	1 (4.2)
Reproductive system and breast disorders	1 (8.3)	-	1 (4.2)
Dysmenorrhoea	1 (8.3)	-	1 (4.2)
Respiratory, thoracic and mediastinal disorders	3 (25)	1 (8.3)	4 (16.7)
Chronic obstructive pulmonary disease	1 (8.3)	.	1 (4.2)
Pharyngolaryngeal pain	2 (16.7)	1 (8.3)	3 (12.5)
Skin and subcutaneous tissue disorders	1 (8.3)	1 (8.3)	2 (8.3)
Dermatitis allergic	-	1 (8.3)	1 (4.2)
Eczema	1 (8.3)	-	1 (4.2)
Rash	-	1 (8.3)	1 (4.2)
Vascular disorders	1 (8.3)	1 (8.3)	2 (8.3)
Hypertension	1 (8.3)	1 (8.3)	2 (8.3)

Adverse events and serious adverse events are not separated out.
N = number of subjects in each group; n = number of subjects with adverse events.

Treatment-Related TEAEs: Treatment-related TEAEs reported during the study are summarized in Table 12.

Table 12. Treatment-Emergent Treatment-Related Adverse Events

System Organ Class Preferred Term	50 mg/Week Etanercept N=12 n (%)	Placebo N=12 n (%)	Total N=24 n (%)
Any adverse events	10 (83.3)	6 (50.0)	16 (66.67)
Gastrointestinal disorders	1 (8.3)	1 (8.3)	2 (8.33)
Abdominal pain upper	1 (8.3)	-	1 (4.17)
Nausea	-	1 (8.3)	1 (4.17)
General disorders and administration site conditions	5 (41.7)	1 (8.3)	6 (25.00)
Asthenia	1 (8.3)	1 (8.3)	2 (8.33)
Fatigue	1 (8.3)	-	1 (4.17)
Injection site hypersensitivity	1 (8.3)	-	1 (4.17)
Injection site pruritus	1 (8.3)	-	1 (4.17)
Injection site reaction	1 (8.3)	-	1 (4.17)
Infections and infestations	5 (41.7)	1 (8.3)	6 (25.00)
Bronchitis	-	1 (8.3)	1 (4.17)
Cellulitis	1 (8.3)	-	1 (4.17)
Influenza	1 (8.3)	-	1 (4.17)
Nasopharyngitis	1 (8.3)	-	1 (4.17)
Pharyngitis	1 (8.3)	-	1 (4.17)
Rhinitis	1 (8.3)	-	1 (4.17)
Tracheitis	1 (8.3)	-	1 (4.17)
Injury, poisoning and procedural complications	-	1 (8.3)	1 (4.17)
Procedural headache	-	1 (8.3)	1 (4.17)
Nervous system disorders	1 (8.3)	1 (8.3)	2 (8.33)
Headache	1 (8.3)	1 (8.3)	2 (8.33)
Psychiatric disorders	1 (8.3)	-	1 (4.17)
Restlessness	1 (8.3)	-	1 (4.17)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	1 (8.3)	3 (12.50)
Pharyngolaryngeal pain	2 (16.7)	1 (8.3)	3 (12.50)
Skin and subcutaneous tissue disorders	1 (8.3)	1 (8.3)	2 (8.33)
Eczema	1 (8.3)	-	1 (4.17)
Rash	-	1 (8.3)	1 (4.17)

Adverse events and serious adverse events are not separated out.
N = number of subjects in each group; n = number of subjects with adverse events.

Serious AEs (SAEs): One subject reported SAEs during this study. This subject received etanercept and reported 2 SAEs: tonsillitis (sore throat coded as pharyngolaryngeal pain), which resolved after treatment given during hospitalization, and subsequent foot cellulitis, which led to early withdrawal from the study.

Death: No death was reported during the study.

Discontinuation From the Study Due to AEs: One subject in the etanercept group withdrew from the study because of an SAE (ie, a serious infection which required treatment with a parenteral antimicrobial agent).

Other Safety-Related Findings: Potentially clinically important (PCI) change in laboratory test results identified in 4 subjects and PCI vital signs were not of clinical importance.

CONCLUSIONS:

This study is the first randomized, placebo-controlled study of an anti-TNF agent, etanercept, for the treatment of SpA subjects with refractory heel enthesitis. This study demonstrated significant clinical benefits and confirmed the good safety profile of etanercept in this population.

Of the 24 enrolled subjects (men 67%, mean age (±SD) 37.3±11.5 years old, 70.8% B27-positive), 12 received etanercept 50 mg, once weekly and 12 received placebo. Both groups were generally similar in terms of demographic characteristics and symptomatic activity of disease at baseline. During the study, 5 subjects withdrew from the study (3 subjects in the placebo group due to lack of efficacy, 1 subject in the placebo group due to lack of compliance, and 1 subject in the etanercept group due to a right foot cellulitis). The 24 enrolled subjects were included in the efficacy and safety analyses.

A total of 19 subjects who presented with positive MRI heel enthesitis defined by a bone marrow edema in the calcaneus, adjacent to the insertion of either Achilles tendon (posterior edema) or fascia plantaris (inferior edema) according to the central radiologist, were included in an additional analysis population.

The observed treatment effect of etanercept on PGA of disease activity was similar to that expected, with the primary endpoint being supported by statistically significant results in favor of etanercept in many of the secondary endpoints.

- Primary efficacy endpoints: the mean (95% CI) normalized net incremental AUC for the PGA of disease activity during 12-weeks-treatment period showed a significant difference between the etanercept and placebo groups (adjusted means: -28.5 [-39.4; -17.7] and -11.1 [-21.9; -0.3], respectively, p-value=0.029).

- Absolute changes between Baseline and Week 12 also showed statistically significant differences in favor of etanercept versus placebo for the PGA of disease activity (adjusted means: -37.6 [-50.5; -24.7] versus -11.6 [-24.5; 1.3], p-value=0·007) with significant change from Baseline observed from Week 8.

- Two-thirds of subjects (66.7%) treated with etanercept achieved a PGA response (defined as ≥50% improvement [decrease] from Baseline) at Week 4 compared with 8.3% in the placebo group (p-value=0.011) which was maintained until Week 12 (66.7% versus 16.7%, respectively, p-value=0.020).

- Statistically significant differences between etanercept and placebo were reported for the change in heel pain from Baseline to Week 8 (adjusted change from Baseline: -36.1 [-50.1; -22.1] versus -10.5 [-24.5; 3.5], p-value=0.013) and to Week 12 (-36.7 [-50.7; -22.7] versus -13.1 [-27.1; 1.0], p-value=0.022).

- Absolute changes between Baseline and Week 12 also showed statistically significant differences in favor of etanercept versus placebo for WOMAC function subscale (-23.2 [-32.5; -13.9] versus -7.8 [-17.1; 1.5], p-value=0.024).

- The response rate "very or moderately important improvement" of the MCII was statistically higher in the etanercept group versus placebo group MCII at Week 12: 75.0% versus 22.2% subjects very or moderately improved (p-value=0.020).

- No subject in the placebo group reported a sustained acceptable symptom state (PASS), when the median time to reach such status in the etanercept group was 3.9 weeks (95% CI= [2.1; not applicable]; p-value=0.0168 from a log-rank test).

- Absolute changes between Baseline and Week 12 showed numerical, but not significant, differences in favor of etanercept versus placebo for BASDAI (adjusted change from baseline: -19.8 [-32.0; -7.7] versus -4.6 [-17.4; 8.1], p-value=0.090), and MASES enthesitis index (-0.55 [-1.48; 0.37] versus 0.13 [-0.79; 1.06], p-value=0.296).

No statistically significant differences were noted in the Achilles tendon or fascia plantaris for the continuous criteria assessed on MRI images (insertion thickness and edema extension) in terms of absolute changes from baseline. However, there was a trend towards an improvement in all 6 MRI scoring systems in subjects receiving etanercept compared with placebo (eg, for 7-grade scale scoring system: placebo adjusted change from Baseline: -0.50 [-1.53; 0.53] and etanercept adjusted change: -1.00 [-1.92; -0.08] and targeted bone edema: placebo mean change: -5.56 [-17.81; 6.70] and etanercept mean change: -6.96 [-17.91; 4.00]). The lack of statistically significant difference in the MRI findings can be explained by the short duration of the study.

The safety results were as follows:

- 22 (91.7 %) subjects; ie, 11 subjects per treatment group, reported TEAEs.

- The TEAEs reported by the highest percentage of subjects were general disorders and administration site conditions, infections and infestations and gastrointestinal disorders.

- A total of 10 subjects in the etanercept group and 6 patients in the placebo group experienced at least 1 AE which was deemed to be related to the study treatment.

- One subject receiving etanercept was withdrawn from the study due to a safety-related AE (foot cellulitis). This subject experienced 2 SAEs during the study:

a tonsillitis (sore throat coded as pharyngolaryngeal pain), which resolved after adapted treatment during hospitalization, and a subsequent foot cellulitis, which led to withdrawal from the study.

The results are of high clinical relevance as they demonstrate a marked symptomatic treatment effect both on primary and secondary endpoints, supported by MRI findings. Treatment with etanercept resulted in significant improvement in PGA of disease activity over 12 weeks, accompanied by significant improvement in secondary outcomes from 8 weeks (decrease in heel pain and disability, improvement in subjects' reported outcomes [MCII and PASS]). Although the study was not designed to assess the potential toxicity of etanercept, no unexpected AE was observed.

In summary, this is the first prospective, randomized, placebo-controlled study in enthesiopathy related to SpA to demonstrate a symptomatic, clinically-relevant, and statistically-significant benefit of etanercept in subjects with refractory disabling heel enthesitis.