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

PROTOCOL NO.: B1801132

PROTOCOL TITLE: A Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate the Non Steroidal Anti-Inflammatory Drugs (NSAID) Sparing Effect of Etanercept in Adult Subjects With Axial Involvement of Spondyloarthritis

Study Centers: Nineteen centers in France took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 05 May 2011 to 03 April 2013.

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

To compare the NSAID sparing effect of etanercept (ETN) with that of placebo in adult subjects with axial involvement of spondyloarthritis (SpA) after 8 weeks of active treatment in comparison to Baseline (NSAID Assessment of the SpondyloArthritis International Society [ASAS] score).

Secondary Objectives:

To determine:

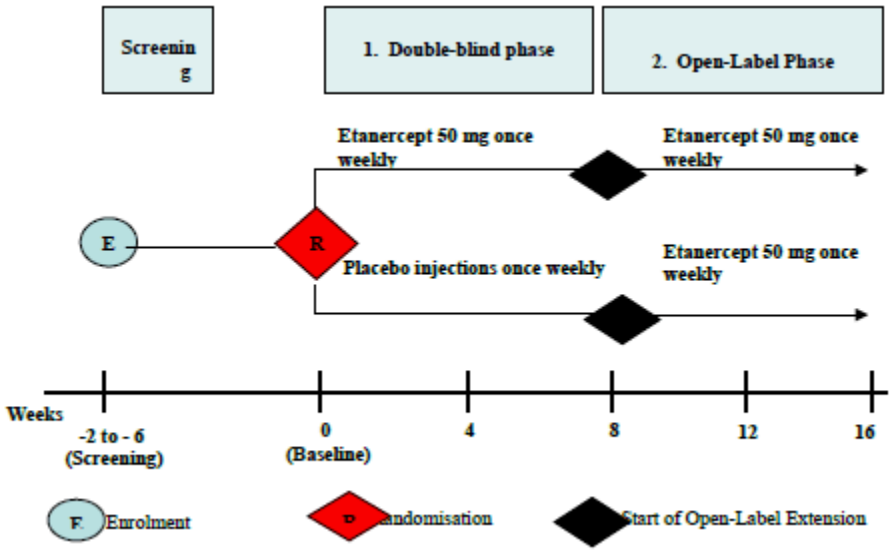
- The area under the curve (AUC) between randomization and Week 8 for the NSAID ASAS score;
- The efficacy of ETN for symptom control compared with that of placebo at Weeks 4 and 8;
- The change in concomitant NSAID treatment requirement between Baseline and Week 16 in the group originally receiving ETN;
- The change in concomitant NSAID treatment requirement between Week 8 and Week 16 in the group originally receiving placebo.

METHODS

Study Design: This was a Phase 4 multicenter, prospective study to evaluate the NSAID sparing effect of ETN in adult subjects with axial involvement of SpA in an out-patient setting.

As shown in Figure 1, the study consisted of an 8-week double-blind (DB), placebo-controlled phase that was followed by an 8-week open-label (OL) phase. Eligible subjects were randomly assigned (1:1 ratio) to receive either ETN 50 mg or placebo once weekly.

Figure 1. Overview of Study Design



At the Week 4 visit, subjects were allowed to enter an Escape Arm (receiving OL ETN 50 mg injections once weekly for 4 weeks) if the total back pain increased >50% or the Bath Ankylosing Spondylitis Disease Activities Index (BASDAI) score increased >50% versus Baseline, and if the subject was receiving NSAIDs at the maximum tolerated dosage (MTD). From Week 8, they received ETN as part of the OL phase.

The maximum treatment duration was 26 weeks, including Screening (at -2 to -6 weeks before Baseline), 8 weeks DB phase, 8 weeks OL phase and a Safety Follow-up Visit at 4 weeks after the last treatment.

Table 1 describes the Schedule of Activities.

Table 1. Schedule of Activities

Study Procedures	DB Placebo-Controlled Period				Open Period	
	Screening[a]	Baseline Week 0	Weeks 4 Visit[b]	Week 8 or Early Discontinuation Visit[b]	Week 12, 16 or Early Discontinuation Visit[b]	Safety Follow-Up Visit by Phone[c]
Visit window			±4 days	±4 days	±4 days	±4 days
Signed informed consent	X					
Demographics	X					
Inclusion/exclusion	X	X				
Prior medications	X	X				
Medical history	X	X				
Cardiovascular diagnosis and family history	X					
Concomitant medications		X	X	X	X	
General physical examination	X	X	X	X	X	
Vital signs (sitting blood pressure, pulse rate and weight)[d]	X	X	X	X	X	
Joint assessment[e]	X	X	X	X	X	
Dactylitis assessment[e]	X	X	X	X	X	
Enthesis assessment[e]	X	X	X	X	X	
Assessment of extra-spinal and extra-articular involvement (IBD, uveitis, psoriasis)[f]	X	X	X	X	X	
Chest X–ray film/TB testing[g]	X					
Fasting metabolic biomarkers/cardiovascular labs/urinalysis		X		X		
HLA B27[h]	X					
Serum and/or urinary pregnancy test[i]	X	X				
Chemistry/haematology/urinalysis	X	X	X	X	X	
C-reactive protein, ESR	X	X	X	X	X	
DKK-1, sclerostin[j]		X		X		
BAS-G		X	X	X	X	
Physician global assessment		X	X	X	X	
Nocturnal and total back pain		X	X	X	X	
BASFI		X	X	X	X	
BASDAI[k]	X	X	X	X	X	
BASMI and chest expansion test		X	X	X	X	
AS WIS questionnaire		X		X	X	
MCII/MCID			X	X	X	
PASS		X	X	X	X	

Table 1. Schedule of Activities

Study Procedures	DB Placebo-Controlled Period				Open Period	
	Screening[a]	Baseline Week 0	Weeks 4 Visit[b]	Week 8 or Early Discontinuation Visit[b]	Week 12, 16 or Early Discontinuation Visit[b]	Safety Follow-Up Visit by Phone[c]
AEs[l]	X	X	X	X	X	X
Dispense diary cards	X	X	X	X	X	
Dispense study drug supplies		X	X	X	X	
Collect diary cards		X	X	X	X	
Test article accountability			X	X	X	

AE = Adverse event; ASAS = Assessment of the SpondyloArthritis International Society; AS WIS = Ankylosing Spondylitis Work Instability Scale; BASDAI = Bath Ankylosing Spondylitis Disease Activities Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BAS-G = Bath Ankylosing Spondylitis – Global Score; BASMI = Bath Ankylosing Spondylitis Metrology Index; DB = Double-blind; DKK-1 = Dickkopf-1; ESR = Erythrocyte sedimentation rate; HLA B27 = Human leukocyte antigen-B27; IBD = Inflammatory bowel disease; MCII/MCID = Minimum Clinically Important Improvement/Minimum Clinically Important Deterioration; PASS = Patient Acceptable Symptom State; PPD = Purified protein derivative; SAE = Serious adverse event; TB = Tuberculosis; TNF = Tumor necrosis factor.

a. At least 2 weeks and not more than 6 weeks before the Baseline Visit.
b. Visit Window: the visit window for Weeks 4, 8, 12, 16 and follow-up was ±4 days.
c. Evaluation performed to follow-up on AEs, approximately 28 days after last dose by telephone.
d. Vital Signs/Height and Weight: The weight was obtained at each visit; height was obtained at the Screening Visit.
e. Swollen and tender 44 joint count, dactylitis and enthesiopathy were performed at each visit to assess peripheral joint involvement according to ASAS recommendation. It was recommended that the same qualified personnel complete these assessments at each visit.
f. Assessment of extra-spinal and extra-articular involvement (IBD, uveitis, psoriasis) were performed at each visit (for the technique of collection of IBD, uveitis and psoriasis). It was recommended that the same qualified personnel complete these assessments at each visit.
g. Chest X-ray film within 3 months of pre study Screening. If the subject was known to be PPD positive, the test was not repeated if documentation was available to show the subject met local criteria for anti-TNF therapy and had not had active TB in the last 2 years. If the subject had a documented negative PPD or Quantiferon test within 3 months prior to the Screening Visit, the test was not repeated.
h. Waived if results were known and copy of laboratory report was in source documents.
i. Women of childbearing potential had a negative serum test at Screening and negative urinary test at the Baseline Visit. The pregnancy tests were repeated at the discretion of the Investigator if subject missed a menses, or if the potential of pregnancy was suspected. If any urinary pregnancy test was positive, a serum pregnancy test was performed.
j. DKK-1 and Sclerostin were measured at Baseline and Week 8. The second test was not required for those subjects who dropped before Week 8.
k. The 48 hour recall period for BASDAI was recorded at each visit from Baseline.
l. Both SAEs and AEs (related and non-related) were reported from the point of signing the informed consent form.

Number of Subjects (Planned and Analyzed): Approximately 80 subjects (40 subjects per treatment group) were planned for this study at approximately 20-25 sites.

A total of 128 subjects were screened at 19 centers in France, 90 subjects were randomized and treated: 42 subjects to DB ETN 50 mg and 48 subjects to the placebo. Four subjects who were randomized to placebo in the DB phase were withdrawn during that phase, did not enter the Escape Arm, and thus never received ETN.

Diagnosis and Main Criteria for Inclusion:

Male and non-pregnant female subjects, aged 18 years and over, with a diagnosis of SpA (as defined by the ASAS criteria for axial SpA), axial involvement refractory to previous or current intake of NSAIDs (defined as at least 2 NSAIDs at MTD determined from past medical history taken for a duration of >1 month [for both NSAIDs combined] before the Screening Visit), and active axial involvement defined by mini BASDAI, who had a current intake of NSAIDS of at least 5 days per week, at 2/3 of the maximum licensed dosage during the 4 weeks before the Screening Visit and during the 1 week before the Baseline Visit were included in the study.

Excluded were subjects who had received any previous treatment with ETN, other tumor necrosis factor α inhibitors, or biologic agents, with a known or expected allergy, contraindication, or hypersensitivity to ETN or its excipients, received prednisone >10 mg/day (or equivalent) or received intra-articular, subcutaneous (SC), intramuscular, intravenous treatment with corticosteroids within 6 weeks prior to Screening.

Study Treatment: ETN was provided as 1.0 mL (50 mg/mL) pre-filled syringes with corresponding matching placebo by the Sponsor. Pre-filled syringes were supplied as appropriate for the treatment arm and sequence to which the subject was randomized.

ETN and placebo SC injections were administered at approximately the same time of day (±4 hours) and on the same day of the week. Each dose of test article was administered as 1 SC injection. It was not administered consecutively in the same anatomical location. Instead, alternate sites (arms, thighs, abdomen, left/right) were used for each administration.

Efficacy and Heath Outcomes Assessment Endpoints:

Primary Efficacy Endpoint: The primary endpoint of this study was the change from Baseline to Week 8 of the NSAID ASAS score, calculated during the week prior to Baseline and during the week prior to the Week 8 visit.

Secondary Efficacy Endpoints: The secondary efficacy endpoints were:

- NSAID intake (NSAID ASAS score) calculated during the 8 weeks of the study;
- Percentage of subjects no longer requiring NSAIDs at Week 8;
- AUC of the mini BASDAI between Baseline and Week 8;

- Change in BASDAI at Weeks 4, 8, 12, 16;
- BASDAI 50 response at Weeks 4, 8, 12, 16;
- ASAS 20, ASAS 40 and 70 response at Weeks 4, 8, 12, 16;
- Change in Ankylosing Spondylitis Disease Activity Score (ASDAS) (C-reactive protein [CRP]/erythrocyte sedimentation rate [ESR]) at Weeks 4, 8, 12, 16;
- Change in CRP/ESR at Weeks 4, 8, 12, 16;
- Change in NSAID score from Baseline to Week 16 (ETN arm);
- Change in NSAID score from Week 8 to Week 16 (placebo arm);
- Change in mini BASDAI score at Weeks 4, 8, 12, 16;
- Extra spinal and extra articular involvement.

Health Outcomes Assessment Endpoints: The health outcomes assessment endpoints were:

- Ankylosing Spondylitis Work Instability Scale (AS WIS);
- Safety endpoints: Safety endpoints assessed were physical examination, vital signs, hematology, chemistry, lipid profile, urinalysis, premature withdrawal, adverse events (AEs) and serious adverse events (SAEs) during the study.

Safety Evaluations: The safety analysis was based on the safety population. Subject safety data were analyzed according to treatment actually received prior to recording of the safety data at each respective study visit.

Statistical Methods: All statistical testing, unless otherwise stated, were 2-sided and conducted at the 5% level, confidence intervals (CI) were 2-sided 95% CIs.

Full Analysis Set: The Intent-To-Treat (ITT) population comprised of all subjects who received at least 1 dose of the randomized treatment. The efficacy analysis were based on the ITT population. Subjects were analyzed according to treatment randomized. Any data recorded after entry into the Escape Arm was included in the analysis of the data for the treatment randomized.

Per Protocol Analysis Set: The Per Protocol analysis (PPAS) population comprised of all subjects in the Full Analysis set (FAS) that did not deviate sufficiently from the protocol as to impact on the efficacy endpoints.

Safety Analysis Set: The safety population comprised of all subjects who received at least 1 dose of randomized treatment. The safety analysis was based on the safety population. Subject safety data was analyzed according to treatment actually received prior to recording of the safety data at each respective study visit.

Analysis of Primary Efficacy Endpoint:

The primary endpoint was the change in NSAID score from Baseline to Week 8, where the Week 8 score corresponded to the NSAID score in the week before the Week 8 visit.

The primary analysis of the primary endpoint was an analysis of covariance (ANCOVA) with Baseline NSAID Score and treatment as explanatory variables. The primary analysis was performed on the ITT population.

Analysis of Secondary Efficacy Endpoints:

All secondary analyses were run on the ITT analysis set. Change in NSAID ASAS score endpoints were repeated on the PPAS.

The total NSAID score from Baseline to Week 8 was analyzed for the primary endpoint using ANCOVA as the main analysis.

The percentage of subjects no longer requiring NSAIDs at Week 8 (ie, in the week before the Week 8 visit) was analyzed using logistic regression. Baseline NSAID Score was included in the model.

An AUC for the first 8 weeks of randomized treatment using the linear trapezoidal rule was calculated for the BASDAI and mini BASDAI and analyzed using ANCOVA and the respective baseline values included as explanatory variables.

The changes from Baseline in the BASDAI individual component questions were also analyzed in the same way as for the BASDAI endpoint.

Partial Remission by Week 8 was analyzed using a logistic regression to assess treatment effect. Baseline variables to be included in this model were Baseline (BASDAI) morning stiffness score and treatment. The 95% exact CIs were reported for the percentages of subjects with and without partial remission at each visit.

The binary response outcomes of BASDAI 50 and ASAS 20, ASAS 40, ASAS 70, and PASS were similarly analyzed.

The changes from Baseline in the continuous endpoints of BASDAI, mini BASDAI, the ASDAS CRP and ASDAS ESR were analyzed using analogous methods to those detailed above for NSAID score. The respective Baseline Scores were used.

The change in NSAID score from Baseline to Week 16 was analyzed for the treatment group starting on ETN using linear regression with Baseline NSAID Score (which was centered around the mean Baseline NSAID score) as the explanatory variable. The Wilcoxon signed rank test and corresponding 95% Hodges Lehmann CI was also generated.

The change in NSAID score from Week 8 to Week 16 was similarly analyzed for the treatment group starting on placebo, with the Week 8 NSAID score used as the "Baseline" explanatory variable.

The total NSAID score for the first 8 weeks of randomized treatment was calculated as an AUC using the linear trapezoidal rule. Last observation carried forward (LOCF) was only applied where the subject was still in the study and the NSAID score was missing. Subjects who were prematurely discontinued from the study were included up to their discontinuation visit.

Extra-spinal and extra-articular involvement data collected at each visit were summarized. In particular, incidence of uveitis, inflammatory bowel disease (IBD) and psoriasis (whether newly occurring or present prior to start of study) were summarized.

Analysis of Health Outcomes Assessment Endpoints:

The AS WIS was analyzed at Week 8 and Week 16 using ANCOVA (only at Week 8) and regression methods.

Safety:

The safety data including vital signs, hematology, chemistry and urinalysis were summarized by treatment received (prior to the recording of the data) for each visit. Data recorded after entry to the Escape Arm and after Week 8 (assuming subject has received ETN) were summarized under ETN in separate summaries. The changes from Baseline in systolic blood pressure (BP) and diastolic BP were analyzed using ANCOVA (at Week 8 only and using the respective Baseline Scores).

Subjects were analyzed according to treatment received prior to Week 8; subjects entering the Escape Arm were included in the ETN treatment group. Withdrawal from the study was summarized according to whether withdrawal was up to or after the Week 8 visit.

AEs were summarized by treatment received (prior to the start of AE) over the whole study duration. AEs occurring after entry to the Escape Arm and after Week 8 (assuming subject has received ETN) were summarized under ETN in a separate summary. AEs were also summarized by treatment group, corresponding only to the period of the study where the subjects were still receiving randomized blinded treatment. This was based on all AEs starting up to entry to the Escape Arm and the Week 8 visit.

A 3 tier approach was used to summarize AEs. Each presentation included relative risk and its associated 95% CI.

Safety summaries and presentations for laboratory parameters, AEs and SAEs were based on Sponsor Data Standards. Separate summaries were presented for data recorded while subjects received randomized study medication (up to Week 8), and data recorded while subjects received OL study medication (following Week 8 or entry into the Escape Arm).

RESULTS

Subject Disposition and Demography: A total of 128 subjects were screened and 90 subjects were assigned to treatment and treated, 42 subjects to the DB ETN 50 mg to OL ETN 50 mg group and 48 subjects to the placebo to OL ETN 50 mg group. Four subjects

who were randomized to receive placebo in the DB phase were withdrawn during this phase, and they did not enter the Escape Arm. These 4 subjects never received ETN. More subjects in the DB ETN 50 mg to OL ETN 50 mg group than in the placebo to OL ETN 50 mg group completed the DB treatment period to OL treatment period (29 [69%] versus 30 [63%] subjects). Fewer subjects in the DB ETN 50 mg to OL ETN 50 mg group than in the placebo to OL ETN 50 mg group entered the Escape Arm (6 [14%] versus 11 [23%]). The study was discontinued by 9 (21%) subjects in the DB ETN 50 mg to OL ETN 50 mg group and by 7 (15%) subjects in the placebo to OL ETN 50 mg group.

All 90 subjects assigned and treated were included in the ITT and MITT populations, and were analyzed for safety. The PPAS population included 22 (52%) subjects of the DB ETN 50 mg to OL ETN 50 mg group and 15 (31%) subjects of the placebo to OL ETN 50 mg group. The subject evaluation groups for all subjects enrolled are presented in Table 2.

Table 2. Subject Evaluation Groups – All Subjects Enrolled

	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Assigned to study treatment	42	48
Treated	42 (100.0%)	48 (100.0%)
Completed study	33 (78.6%)	41 (85.4%)
Completed DB treatment period	33 (78.6%)	33 (68.8%)
Entered Escape Arm and completed study	4 (9.5%)	11 (22.9%)
Completed DB to OL treatment period	29 (69.0%)	30 (62.5%)
Discontinued	9 (21.4%)	7 (14.6%)
Withdrawn during DB treatment period	3 (7.1%)	4 (8.3%)
Withdrawn during OL having completed DB treatment period	4 (9.5%)	3 (6.3%)
Withdrawn during OL having entered Escape Arm	2 (4.8%)	0
Ongoing at date of cut-off	0	0
ITT population	42 (100.0%)	48 (100.0%)
MITT population	42 (100.0%)	48 (100.0%)
PPAS population	22 (52.4%)	15 (31.3%)
Entered Escape Arm	6 (14.3%)	11 (22.9%)
Entered OL treatment period	33 (78.6%)	33 (68.8%)
Analyzed for safety		
Adverse events	42 (100.0%)	48 (100.0%)
Laboratory data	42 (100.0%)	48 (100.0%)

Discontinuations attributed to the last study treatment received.
DB = Double-blind; ETN = Etanercept; ITT = Intent-to-treat; MITT = Modified intent-to-treat; OL = Open-label; PPAS = Per protocol analysis set.

During both treatment periods, discontinuations from study were reported by more subjects in the DB ETN 50 mg to OL ETN 50 mg group (9 [21%] subjects) than in the placebo to OL ETN 50 mg group (7 [15%] subjects). Herein, discontinuations due to non AEs were reported by 12% of subjects in the DB ETN 50 mg to OL ETN 50 mg group and 8% of subjects in the placebo to OL ETN 50 mg group. Discontinuations due to AEs related to study drug were reported in 1 subject in both the DB ETN 50 mg to OL ETN 50 mg group and in the placebo to OL ETN 50 mg group; discontinuations due to AEs not related to study

drug were reported by more subjects in the DB ETN 50 mg to OL ETN 50 mg group (3 [7%] subjects) than in the placebo to OL ETN 50 mg group (2 [4%] subjects).

During the DB treatment period, discontinuations from study were similar between the DB ETN 50 mg to OL ETN 50 mg group and the placebo to OL ETN 50 mg group (3 [7%] subjects versus 4 [8%] subjects, respectively). During the OL treatment period, discontinuations from study were reported by more subjects in the DB ETN 50 mg to OL ETN 50 mg group (4 [12%] subjects) than in the placebo to OL ETN 50 mg group (3 [9%] subjects].

Regarding subjects having entered the Escape Arm, 2 of 6 subjects of the DB ETN 50 mg to OL ETN 50 mg group discontinued the study, 1 subject due to a protocol violation and 1 subject due to AE not related to study drug. None of 11 subjects in the placebo to OL ETN 50 mg group discontinued study.

A summary of discontinuations from study during all treatment periods for the safety population is provided in Table 3.

Table 3. Discontinuation From Study – Safety Population

	DB ETN 50 mg to OL ETN 50 mg N=42	Placebo to OL ETN 50 mg N=48
Discontinuations	9 (21.4%)	7 (14.6%)
Non-adverse events discontinuations	5 (11.9%)	4 (8.3%)
Does not meet entrance criteria	0	1 (2.1%)
Insufficient clinical response	0	1 (2.1%)
Lost to follow-up	2 (4.8%)	0
Other	2 (4.8%)	1 (2.1%)
Protocol violation	1 (2.4%)	1 (2.1%)
Related to study drug	1 (2.4%)	1 (2.1%)
Adverse event	1 (2.4%)	1 (2.1%)
Not related to study drug	3 (7.1%)	2 (4.2%)
Adverse event	3 (7.1%)	2 (4.2%)

DB ETN = Double-blind etanercept; N = Number of subjects; OL ETN = Open-label etanercept.

The mean age of all subjects was 39 years old; most of the subjects were male (56 of 90 subjects), and white. Demographic data are presented in Table 4.

Table 4. Demographic Characteristics – ITT Population

	DB ETN 50 mg to OL ETN 50 mg N=42	Placebo to OL ETN 50 mg N=48	Total N=90
Age (years)			
N	42	48	90
18-44	31	32	63
45-64	9	15	24
≥ 65	2	1	3
Mean	38.8	38.9	38.9
SD	12.3	11.4	11.8
Range	19-67	18-67	18-67
Gender			
N	42	48	90
Female	18	16	34
Male	24	32	56
Race			
N	42	48	90
White	40	48	88
Black	1	0	1
Other	1	0	1
Weight (kg)			
N	42	48	90
Mean	73.8	75.4	74.7
SD	14.2	15.2	14.7
Range	53-114	54-108	53-114
Height (cm)			
N	42	46	88
Missing	0	2	2
Mean	169.7	171.0	170.4
SD	9.1	9.2	9.1
Range	155-196	152-189	152-196
Body mass index (kg/m²)			
N	42	46	88
Missing	0	2	2
Mean	25.7	25.9	25.8
SD	4.8	4.9	4.9
Range	19-40	19-42	19-42

DB ETN = Double-blind etanercept; ITT = Intent-to-treat; N = Number of subjects; OL ETN = Open-label etanercept; SD = Standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

The primary endpoint of this study was the change from Baseline to Week 8 of the NSAID ASAS score calculated during the week prior to Baseline and during the week prior to the Week 8 visit.

The primary analysis of change from Baseline in NSAID ASAS Score at Week 8 showed a −27.27 (95% CI: −44.17, −10.38) point difference from the placebo, indicating a beneficial effect of ETN relative to placebo. This difference was statistically significant (p = 0.0019) (Table 5).

Table 5. Primary Analysis: Change From Baseline in NSAID ASAS Score at Week 8 – ANCOVA (LOCF and Imputation) ITT Population

Treatment Group	Number of Subjects N	Adjusted Mean (SE) of Changes Within Group*	Adjusted Difference of Mean Changes Between Groups[a] (95% CI)	Between Group p-Value*
DB ETN 50 mg to OL ETN 50 mg	39	-63.90 (6.09)	-27.27 (-44.17, -10.38)	0.0019
Placebo to OL ETN 50 mg	42	-36.63 (5.87)		

Only subjects with non-missing change from Baseline Value are included for post Baseline Visits.
ANCOVA = Analysis of covariance; ASAS = Assessment of the SpondyloArthritis International Society; CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward; N = Subjects evaluable for adverse events; NSAID = Non-steroidal anti-inflammatory drug; OL ETN = Open-label etanercept; SE = Standard error.

a. ANCOVA model on change from Baseline NSAID Score fitting Baseline NSAID Score as a covariate, plus treatment as a factor.

Secondary Efficacy Endpoints:

Total NSAID ASAS (AUC) Score From Baseline to Week 8:

The total NSAID ASAS (AUC) score from Baseline to Week 8 using ANCOVA (with LOCF and imputation of missing diary data) showed a −19.78 (95% CI: −34.99, −4.57) point difference between ETN and placebo. This indicated a statistically significant beneficial effect of ETN relative to placebo (p = 0.0115).

The analysis of total NSAID ASAS (AUC) score from Baseline to Week 8 at Week 8 using ANCOVA (with LOCF and imputation of missing diary data) is provided in Table 6.

Table 6. Total NSAID ASAS (AUC) Score From Baseline to Week 8 (LOCF) – ANCOVA ITT Population

Time on Therapy	Therapy Group	Number of Subjects	Raw Mean Score (SD)	Adjusted Mean (SE) of Raw Score*	Within Group p-Value[a]	Adjusted Difference of Mean Between Groups*	95% CI on Adjusted Difference Between Groups*	Between Group p-Value*
Baseline to Week 8	DB ETN 50 mg to OL ETN 50 mg	40	46.21 (36.69)	45.24 (5.44)	<0.0001	-19.78	(-34.99, -4.57)	0.0115
	Placebo to OL ETN 50 mg	42	64.10 (32.20)	65.02 (5.30)	<0.0001			

LOCF was only applied where the subject was still in the study and the NSAID score was missing.
ANCOVA = Analysis of covariance; ASAS = Assessment of the SpondyloArthritis International Society; AUC = Area under curve; CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward; NSAID = Non-steroidal anti-inflammatory drug; OL ETN = Open-label etanercept; SD = Standard deviation; SE = Standard error.

a. ANCOVA model used for 'adjusted' values and between group p-values : AUC = Baseline Score + treatment; Adjusted mean change between groups is DB ETN 50 mg to OL ETN 50 mg - placebo to OL ETN 50 mg.

Subjects Using NSAID at Week 8:

The proportion of subjects using NSAIDs at Week 8 was higher in the placebo to OL ETN 50 mg group (32 [80%] subjects) compared to the DB ETN 50 mg to OL ETN 50 mg group (17 [52%] subjects); this difference was statistically significant (p = 0.0066).

The summary of proportion of subjects using NSAIDs at Week 8 using logistic regression (with observed case [OC] and no imputation of missing diary data) is provided in Table 7.

Table 7. Proportion of Subjects Using NSAIDs at Week 8 - Logistic Regression (OC and No Imputation) ITT Population

Week	DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)	Odds Ratio[a]		
			Estimate	(95% CI)	P-value
Week 8	17/33 (51.52%)	32/40 (80.00%)	0.209	(0.07, 0.65)	0.0066

N - The number of subjects with a non-missing Week 8 NSAID score.
n - The number of subjects who have used NSAIDs during the week prior to Week 8 visit.
CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; NSAID = Non-steroidal anti-inflammatory drug; OL ETN = Open-label etanercept; OC = Observed case.
a. Logistic regression with Baseline Score and treatment group included as covariates.

Change in NSAID ASAS Score From Baseline to Week 16:

The within treatment comparison of change in NSAID ASAS score from Baseline to Week 16 for ETN only was statistically significant (65.93 [95% CI: 87.01, 44.85], p <0.0001). This was confirmed when performing a Wilcoxon Rank Sum test to the median change (p <0.0001).

The within treatment comparison of change in NSAID ASAS score from Week 8 to Week 16 for the placebo to OL ETN 50 mg group was statistically significant (39.22 [95% CI: 52.94, 25.49], p <0.0001). This was confirmed when performing a Wilcoxon Rank Sum test to the median change (p = 0.0005).

In the DB ETN 50 mg to OL ETN 50 mg group, change in NSAID ASAS score from Baseline to Week 16 (ETN only) using linear regression (OC and no imputation of missing diary data) is provided in Table 8.

In the placebo to OL ETN 50 mg group, the change in NSAID ASAS score from Week 8 to Week 16 using linear regression (OC and no imputation of missing diary data) is provided in Table 9.

Summaries of the absolute NSAID ASAS score and change from Baseline values for both treatment groups (OC and no imputations of missing diary data) are provided in Table 10 (ITT population) and Table 11 (PPAS population).

Table 8. Change in NSAID ASAS Score From Baseline to Week 16 (Etanercept Only) - Linear Regression (OC and No Imputation) ITT Population

N	Adjusted Mean[a]	S.E. of Adjusted Mean	95% CI	p-Value
25	-65.93	10.19	(-87.01, -44.85)	<0.0001

N is the number used in analysis.
ASAS = Assessment of the SpondyloArthritis International Society; CI = Confidence interval; ITT = Intent-to-treat; NSAID = Non-steroidal anti-inflammatory drug; OC = Observed case; S.E. = Standard Error.
a. Adjusted for Baseline NSAID Score (Centerd around the mean Baseline NSAID score).

Table 9. Change in NSAID ASAS Score From Week 8 to Week 16 (Placebo Only) - Linear Regression (OC and No Imputation) ITT Population

N	Adjusted Mean[a]	S.E. of Adjusted Mean	95% CI	p-Value
17	-39.22	6.44	(-52.94, -25.49)	<0.0001

N is the number used in analysis.
ASAS = Assessment of the SpondyloArthritis International Society; CI = Confidence interval; ITT = Intent-to-treat; NSAID = Non-steroidal anti-inflammatory drug; OC = Observed case; S.E. = Standard Error.
a. Adjusted for Week 8 NSAID Score (Centred around the mean Baseline NSAID score).

Table 10. NSAID ASAS Score - Absolute and Change From Baseline Values (OC and No Imputation) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	41	44		
	Mean	100.3	93.6		
	SD.	36.83	23.3		
	Median	100	100		
	Min	21	29		
	Max	214	152		
Week 4	N	35	38	34	36
	Mean	47.6	57.8	-54.5	-32.9
	SD.	46.41	40.05	54.05	42.21
	Median	50	60.7	-60.7	-11.1
	Min	0	0	-214	-100
	Max	200	129	29	64
Week 8	N	33	40	32	37
	Mean	24.2	56.6	-75.6	-30.9
	SD	33.72	39.53	51.96	41.1
	Median	7.1	58.3	-87.9	-7.1
	Min	0	0	-214	-100
	Max	136	100	29	71
Week 12	N	29	36	28	33
	Mean	28.1	35.6	-69.6	-56.1
	SD	38.54	38.88	54.05	40.08
	Median	1.8	19.6	-87.9	-66.7
	Min	0	0	-214	-110
	Max	107	118	36	21
Week 16	N	25	27	25	25
	Mean	33.4	28.2	-65.9	-63.0
	SD	49.91	39.67	63.30	39.42
	Median	0.0	0.0	-87.5	-75.0
	Min	0	0	-214	-100
	Max	200	100	100	7

NSAID ASAS score for each subject at a particular visit calculated as the mean of the 7 days NSAID dosing prior to the visit.
NSAID ASAS score calculated for an individual subject if at least 5 days of dosing information available.
ASAS = Assessment of the SpondyloArthritis International Society; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; NSAID = Non-steroidal anti-inflammatory drug; OL ETN = Open-label etanercept; OC = Observed case; SD = Standard deviation.

Table 11. NSAID ASAS Score - Absolute and Change From Baseline Values (OC and No Imputation) PPAS Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	22	15		
	Mean	117.1	95.1		
	SD.	35.09	20.11		
	Median	100	100		
	Min	86	67		
	Max	214	150		
Week 4	N	20	11	20	11
	Mean	50.3	41.2	-65.9	-57.4
	SD.	54.08	38.51	56.52	33.52
	Median	42.9	42.9	-72.6	-66.7
	Min	0	0	-214	-100
	Max	200	100	14	0
Week 8	N	19	15	19	15
	Mean	26.7	53	-85.7	-42.1
	SD	39.66	43.29	55.11	42.06
	Median	0	66.7	-92.9	-57.1
	Min	0	0	-214	-100
	Max	136	100	21	0
Week 12	N	17	13	17	13
	Mean	29.0	44.4	-80.9	-51.8
	SD	40.25	40.84	52.03	38.86
	Median	0.0	50.0	-92.9	-50.0
	Min	0	0	-214	-100
	Max	100	118	0	0
Week 16	N	18	8	18	8
	Mean	40.5	19.6	-72.4	-76.2
	SD	55.84	34.04	69.00	33.33
	Median	3.6	5.4	-96.4	-83.9
	Min	0	0	-214	-100
	Max	200	100	100	0

NSAID ASAS score for each subject at a particular visit calculated as the mean of the 7 days NSAID dosing prior to the visit.
NSAID ASAS score calculated for an individual subject if at least 5 days of dosing information available.
ASAS = Assessment of the SpondyloArthritis International Society; DB ETN = Double-blind etanercept; Max = Maximum; Min = Minimum; N = Number of subjects; NSAID = Non-steroidal anti-inflammatory drug; OL ETN = Open-label etanercept; OC = Observed case; PPAS = Per protocol analysis set; SD = Standard deviation.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The ANCOVA analyses for the key secondary endpoint of BASDAI change from Baseline for the ITT population at Week 4 and Week 8 showed a smaller increase in BASDAI score for subjects receiving DB ETN compared to placebo. There was a -0.93 (95% CI: -1.68, -0.18) difference from placebo at Week 4, which was statistically significant

(p = 0.0153), and a -0.88 difference (95% CI: -1.76, -0.00) from placebo at Week 8, which indicated a trend in favor of DB ETN, but was not statistically significant (p = 0.0510) (Table 12). A descriptive summary of the BASDAI absolute and change from Baseline values (OC) at Weeks 4, 8, 12 and 16 are provided in Table 13.

Table 12. BASDAI Change From Baseline at Week 4 and Week 8 – ANCOVA (LOCF) – ITT Population

Time on Therapy	Treatment Group	Number of Subjects N	Adjusted Mean (SE) of Changes Within Group[a]	Adjusted Difference of Mean Changes Between Groups[a] (95% CI)	Between Group p-Value[a]
Week 4	DB ETN 50 mg to OL ETN 50 mg	39	-1.50 (0.27)	-0.93 (-1.68, -0.18)	0.0153
	Placebo to OL ETN 50 mg	44	-0.56 (0.26)		
Week 8	DB ETN 50 mg to OL ETN 50 mg	41	-2.01 (0.32)	-0.88 (-1.76, 0.00)	0.0510
	Placebo to OL ETN 50 mg	45	-1.13 (0.31)		

Only subjects with non-missing change from Baseline value are included for post Baseline Visits.
ANCOVA = Analysis of covariance; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward; N = Subjects evaluable for adverse events; OL ETN = Open-label etanercept; SE = Standard error.

a. ANCOVA model on change from Baseline BASDAI score fitting Baseline BASDAI score as a covariate, plus treatment as a factor.

Table 13. Description of BASDAI Total Score - Absolute and Change From Baseline Values (OC) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	42	48		
	Mean	6	5.9		
	SD.	1.65	1.52		
	Median	6.1	6.2		
	Min	3	3		
	Max	10	10		
Week 4	N	39	44	39	44
	Mean	4.5	5.4	-1.5	-0.5
	SD.	2.17	1.83	2.12	1.44
	Median	4.8	5.3	-1.3	-0.4
	Min	1	2	-6	-7
	Max	9	10	2	2
Week 8	N	37	42	37	42
	Mean	3.9	4.8	-2.1	-1.2
	SD	2.52	2.06	2.37	1.91
	Median	3.6	5.3	-1.5	-0.9
	Min	0	1	-7	-6
	Max	10	9	2	2
Week 12	N	36	41	36	41
	Mean	3.5	3.3	-2.5	-2.6
	SD	2.41	2.25	2.35	2.12
	Median	3.1	3.3	-2.3	-2.2
	Min	0	0	-8	-7
	Max	9	9	2	1
Week 16	N	28	37	28	37
	Mean	3.5	2.9	-2.6	-3
	SD	2.36	2.11	1.83	2.14
	Median	2.4	2.4	-3	-2.5
	Min	1	0	-7	-7
	Max	8	9	1	1

N is the number of subjects with available assessments at the corresponding visit.
Means and Medians have been determined within a subject prior to summarizing across subjects. Baseline is defined to be the latest non-missing value from a range of pre-treatment visits. The minimum and maximum values have been determined from all values recorded.
Unplanned readings have been excluded from the presentation.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; OC = Observed case; OL ETN = Open-label etanercept; SD = Standard deviation.

Mini Bath Ankylosing Spondylitis Disease Activity Index (mini BASDAI):

Descriptive summaries of the mini BASDAI absolute and change from Baseline values (OC) at Weeks 4, 8, 12 and 16 are provided in Table 14.

The summary of mini BASDAI from Baseline to Week 8 (AUC) using ANCOVA is provided in Table 15. Regarding the mini BASDAI Baseline to Week 8 AUC, there was a statistically significant difference compared with placebo ($p = 0.0053$).

Table 14. Description of mini BASDAI Score - Absolute and Change From Baseline Values (OC) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	42	48		
	Mean	6.6	6.6		
	SD	1.61	1.38		
	Median	6.6	6.7		
	Min	4	4		
	Max	10	10		
Week 4	N	39	44	39	44
	Mean	5	6	-1.6	-0.6
	SD	2.2	1.77	2.17	1.6
	Median	5	6	-1.2	-0.3
	Min	1	3	-7	-6
	Max	9	10	2	3
Week 8	N	37	42	37	42
	Mean	4.3	5.4	-2.3	-1.2
	SD	2.55	2.17	2.41	2.02
	Median	4	6	-2	-0.7
	Min	0	1	-8	-6
	Max	10	9	2	2
Week 12	N	36	42	36	42
	Mean	3.7	3.9	-2.8	-2.7
	SD	2.46	2.42	2.31	2.1
	Median	3.3	3.8	-2.5	-2.5
	Min	0	0	-8	-7
	Max	9	9	1	1
Week 16	N	28	37	28	37
	Mean	3.8	3.4	-2.8	-3.2
	SD	2.38	2.34	1.97	2.26
	Median	3	2.8	-2.9	-2.5
	Min	0	0	-7	-7
	Max	8	9	1	0

N is the number of subjects with available assessments at the corresponding visit.
Means and Medians have been determined within a subject prior to summarizing across subjects. Baseline is defined to be the latest non-missing value from a range of pre-treatment visits. The minimum and maximum values have been determined from all values recorded.
Unplanned readings have been excluded from the presentation.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; OC = Observed case; OL ETN = Open-label etanercept; SD = Standard deviation.

Table 15. mini BASDAI Baseline to Week 8 AUC (LOCF) - ANCOVA ITT Population

Time on Therapy	Therapy Group	Number of Subjects	Raw Mean Score (SD)	Adjusted Mean (SE) of Raw Score[a]	Within Group p-Value[a]	Adjusted Difference of Mean Between Groups[a]	95% CI on Adjusted Difference Between Groups[a]	Between Group p-Value[a]
Baseline to Week 8	DB ETN 50 mg to OL ETN 50 mg	41	276.75 (116.23)	275.68 (13.64)	<0.0001	-53.70	(-91.01, -16.38)	0.0053
	Placebo to OL ETN 50 mg	46	328.42 (93.39)	329.37 (12.88)	<0.0001			

Adjusted mean change between groups is DB ETN 50 mg to OL ETN 50 mg - placebo to OL ETN 50 mg.
LOCF was only applied where the subject was still in the study and the mini BASDAI score was missing.
ANCOVA = Analysis of covariance; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL ETN = Open-label etanercept; SE = Standard error; SD = Standard deviation.
a. ANCOVA model on AUC of mini BASDAI from Baseline to Week 8 fitting Baseline mini BASDAI score as a covariate, plus treatment as a factor.

Bath Ankylosing Spondylitis Disease Activities Index 50 (BASDAI 50):

There was a statistically significant difference between subjects in the DB ETN 50 mg to OL ETN 50 mg group and placebo to OL ETN 50 mg group, in favor of ETN, in terms of the proportion of subjects experiencing BASDAI 50 at Week 8 (39% versus 18% for subjects in the DB ETN 50 mg to OL ETN 50 mg group and placebo to OL ETN 50 mg group respectively, p = 0.0324).

For the ITT population, the summary of BASDAI 50 at Week 8 using logistic regression is provided in Table 16 (with LOCF) ; descriptive summaries of the proportions of BASDAI 50 at Weeks 4, Week 8, Week 12 and Week 16 (OC) is provided in Table 17.

Table 16. BASDAI 50 at Week 8 - Logistic Regression (LOCF) ITT Population

Week	DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)	Odds Ratio[a]		
			Estimate	(95% CI)	p-Value
Week 8	16/41 (39.02%)	8/45 (17.78%)	2.963	(1.10, 8.01)	0.0324

N - The number of subjects with a non-missing Week 8 (LOCF) BASDAI score.
n - The number of subjects who are BASDAI 50 Responder at Week 8 visit.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CI = Confidence interval;
DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward;
OL ETN = Open-label etanercept.
a. Logistic regression with Baseline Morning Stiffness Score and treatment group included as covariates.

Table 17. BASDAI 50 - Proportions (OC) ITT Population

Week	DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)
Week 4	10/39 (25.64%)	3/44 (6.82%)
Week 8	14/37 (37.84%)	8/42 (19.05%)
Week 12	17/36 (47.22%)	19/41 (46.34%)
Week 16	15/28 (53.57%)	18/37 (48.65%)

N is the number of subjects with non-missing BASDAI50 response at corresponding visit.
n is the number of subjects who are BASDAI 50 Responder at corresponding visit.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; DB ETN = Double-blind etanercept;
ITT = Intent-to-treat; OC = Observed case; OL ETN = Open-label etanercept.

Assessment of the SpondyloArthritis International Society 20, 40 and 70 (ASAS 20, ASAS 40, and ASAS 70):

There was a statistically significant difference between subjects in the DB ETN 50 mg to OL ETN 50 mg group and placebo to OL ETN 50 mg group at Week 8 in terms of the proportion of subjects experiencing ASAS40 (44% versus 21% for subjects in the DB ETN 50 mg to OL ETN 50 mg group and placebo to OL ETN 50 mg group, p = 0.0284). Although the proportion of subjects experiencing ASAS20 at Week 8, was numerically greater in the DB ETN 50 mg to OL ETN 50 mg group compared to placebo to OL ETN 50 mg group (44% versus 24%), this difference was not statistically significant. No

differences were detected between the 2 treatment groups in terms of the proportion of subjects with ASAS70 at Week 8.

For the ITT population, the summary of ASAS 20, ASAS 40 and ASAS 70 at Week 8 using logistic regression is provided in Table 18 (with LOCF); descriptive summaries of the proportions of ASAS 20, ASAS 40 and ASAS 70 at Weeks 4, Week 8, Week 12, and Week 16 (OC) are provided in Table 19.

Table 18. ASAS 20, ASAS 40, ASAS 70 at Week 8 - Logistic Regression (LOCF) ITT Population

	Week	DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)	Odds Ratio[a]		
				Estimate	(95% CI)	p-Value
ASAS 20	Week 8	16/36 (44.44%)	10/42 (23.81%)	2.696	(1.00, 7.27)	0.0501
ASAS 40	Week 8	16/36 (44.44%)	9/42 (21.43%)	3.103	(1.13, 8.54)	0.0284
ASAS 70	Week 8	5/36 (13.89%)	3/42 (7.14%)	2.130	(0.47, 9.72)	0.3291

N is the number of subjects with non-missing ASAS assessment at corresponding visit.
n is the number of subjects with ASAS response equal to "Yes" at corresponding visit.
ASAS = Assessment of the SpondyloArthritis International Society; CI = Confidence interval;
DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward;
OL ETN = Open-label etanercept.

a. Logistic regression with Baseline Morning Stiffness Score and treatment group included as covariates.

Table 19. ASAS 20, ASAS 40, ASAS 70 - Proportions Over Time (OC) ITT Population

		DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)
ASAS 20	Week 4	14/38 (36.84%)	5/42 (11.90%)
	Week 8	16/36 (44.44%)	10/39 (25.64%)
	Week 12	17/35 (48.57%)	21/37 (56.76%)
	Week 16	18/28 (64.29%)	23/36 (63.89%)
ASAS 40	Week 4	9/38 (23.68%)	3/42 (7.14%)
	Week 8	16/36 (44.44%)	9/39 (23.08%)
	Week 12	17/35 (48.57%)	20/37 (54.05%)
	Week 16	16/28 (57.14%)	20/36 (55.56%)
ASAS 70	Week 4	2/38 (5.26%)	1/42 (2.38%)
	Week 8	5/36 (13.89%)	3/39 (7.69%)
	Week 12	8/35 (22.86%)	7/37 (18.92%)
	Week 16	5/28 (17.86%)	11/36 (30.56%)

N is the number of subjects with non-missing ASAS assessment at each visit.
n is the number of subjects with ASAS response equal to "Yes" at corresponding visit.
ASAS = Assessment of the SpondyloArthritis International Society; DB ETN = Double-blind etanercept;
ITT = Intent-to-treat; OC = Observed case; OL ETN = Open-label etanercept.

Ankylosing Spondylitis Disease Activity Score – C-Reactive Protein (ASDAS CRP):

There were statistically significant differences between ETN and placebo at both Week 4 and Week 8 (-0.78 [95% CI: -1.11, -0.44], p <0.0001 and -0.68 [95% CI: -1.09, -0.28], p = 0.0011, respectively).

For the ITT population, the summary of ASDAS CRP change from Baseline at Week 4 and Week 8 using ANCOVA is provided in Table 20 (with LOCF); descriptive summaries of the ASDAS CRP in terms of absolute and change from Baseline values (OC) at Weeks 4, 8, 12, and 16 are provided in Table 21.

Table 20. ASDAS CRP Change From Baseline at Weeks 4 and 8 - ANCOVA (LOCF) – ITT Population

Time on Therapy	Therapy Group	Number of Subjects	Raw Mean Score (SD)	Adjusted Mean (SE) of Raw Score[a]	Adjusted Mean (SE) of Changes Within Group[a]	95% CI on Adj Mean Changes Within Groups[a]	Within Group p-Value[a]	Adjusted Difference of Mean Changes Between Groups[a]	95% CI on Adjusted Difference Between Groups[a]	Between Group p-Value[a]
Baseline	DB ETN 50 mg to OL ETN 50 mg	42	3.38 (0.95)							
	Placebo to OL ETN 50 mg	43	3.23 (0.82)							
Week 4	DB ETN 50 mg to OL ETN 50 mg	37	2.39 (0.83)	2.35 (0.12)	-0.94 (0.12)	(-1.18, -0.70)	<0.0001	-0.78	(-1.11, -0.44)	<0.0001
	Placebo to OL ETN 50 mg	41	3.10 (0.93)	3.13 (0.11)	-0.16 (0.11)	(-0.39, 0.07)	0.1702			
Week 8	DB ETN 50 mg to OL ETN 50 mg	41	2.13 (0.94)	2.10 (0.14)	-1.21 (0.14)	(-1.50, -0.92)	<0.0001	-0.68	(-1.09, -0.28)	0.0011
	Placebo to OL ETN 50 mg	42	2.74 (1.02)	2.78 (0.14)	-0.53 (0.14)	(-0.81, -0.24)	0.0004			

Adjusted mean change between groups is DB ETN 50 mg to OL ETN 50 mg - placebo to OL ETN 50 mg.
Only subjects with non-missing change from baseline value are included for post Baseline Visits.
ANCOVA = Analysis of covariance; ASDAS = Ankylosing Spondylitis Disease Activity Score; CI = Confidence interval; CRP = C-reactive protein; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL ETN = Open-label etanercept; SD = Standard deviation; SE = Standard error.
a. ANCOVA model on change from Baseline ASDAS CRP Score fitting Baseline ASDAS CRP Score as a covariate, plus treatment as a factor.

Table 21. Description of ASDAS CRP - Absolute and Change From Baseline Values (OC) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	42	43		
	Mean	3.4	3.2		
	SD	0.95	0.82		
	Median	3.4	3.1		
	Min	2	1		
	Max	5	5		
Week 4	N	37	44	37	41
	Mean	2.4	3.1	-1	-0.1
	SD	0.83	0.93	1.03	0.58
	Median	2.5	3.1	-0.8	-0.2
	Min	1	1	-4	-1
	Max	4	6	1	1
Week 8	N	37	40	37	37
	Mean	2.1	2.7	-1.3	-0.5
	SD	0.95	1.04	1.15	1
	Median	2	3	-1.1	-0.4
	Min	0	1	-4	-3
	Max	4	5	1	1
Week 12	N	35	39	35	36
	Mean	2	2	-1.4	-1.2
	SD	0.97	0.93	1.13	1.07
	Median	1.7	2	-1.3	-1
	Min	0	0	-4	-3
	Max	4	5	0	2
Week 16	N	28	36	28	33
	Mean	1.9	1.7	-1.6	-1.5
	SD	0.92	0.86	0.92	1.02
	Median	1.7	1.6	-1.6	-1.3
	Min	1	0	-3	-4
	Max	4	4	0	0

N is the number of subjects with available assessments at the corresponding visit.
Means and Medians have been determined within a subject prior to summarizing across subjects. Baseline is defined to be the latest non-missing value from a range of pre-treatment visits. The minimum and maximum values have been determined from all values recorded.
Unplanned readings have been excluded from the presentation.
ANCOVA = Analysis of covariance; ASDAS = Ankylosing Spondylitis Disease Activity Score; CRP = C-reactive protein; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; OC = Observed case; OL ETN = Open-label etanercept; SD = Standard deviation.

Ankylosing Spondylitis Disease Activity Score – Erythrocyte Sedimentation Rate (ASDAS ESR):

There were statistically significant differences between ETN and placebo at both Week 4 and Week 8 (-0.57 [95% CI: -0.90, -0.24], p = 0.0011 and -0.67 [95% CI: -1.11, -0.22], p = 0.0037, respectively).

For the ITT population, the summary of ASDAS ESR change from Baseline at Week 4 and Week 8 using ANCOVA is provided in Table 22 (with LOCF); descriptive summaries of the ASDAS ESR in terms of absolute and change from Baseline values (OC) at Weeks 4, 8, 12, and 16 are provided in Table 23.

Table 22. ASDAS ESR Change From Baseline at Weeks 4 and 8 - ANCOVA (LOCF) – ITT Population

Time on Therapy	Therapy Group	Number of Subjects	Raw Mean Score (SD)	Adjusted Mean (SE) of Raw Score[a]	Adjusted Mean (SE) of Changes Within Group[a]	95% CI on Adjusted Mean Changes Within Groups[a]	Within Group p-Value[a]	Adjusted Difference of Mean Changes Between Groups[a]	95% CI on Adjusted Difference Between Groups[a]	Between Group p value[a]
Baseline	DB ETN 50 mg to OL ETN 50 mg	37	3.33 (0.89)							
	Placebo to OL ETN 50 mg	37	3.12 (0.77)							
Week 4	DB ETN 50 mg to OL ETN 50 mg	28	2.49 (0.92)	2.42 (0.12)	-0.76 (0.12)	(−1.00, −0.52)	<0.0001	−0.57	(-0.90, −0.24)	0.0011
	Placebo to OL ETN 50 mg	31	2.93 (0.81)	2.99 (0.11)	-0.19 (0.11)	(-0.41,−0.04)	0.1096			
Week 8	DB ETN 50 mg to OL ETN 50 mg	33	2.24 (1.09)	2.18 (0.16)	-1.05 (0.16)	(-1.37, −0.73)	<0.0001	−0.67	(-1.11, −0.22)	0.0037
	Placebo to OL ETN 50 mg	36	2.80 (0.97)	2.85 (0.15)	-0.38 (0.15)	(-0.69, −0.08)	0.0149			

Adjusted mean change between groups is DB ETN 50 mg to OL ETN 50 mg - Placebo to OL ETN 50 mg.
Only subjects with non-missing change from baseline value are included for post Baseline Visits.
ANCOVA = Analysis of covariance; ASDAS = Ankylosing Spondylitis Disease Activity Score; CI = Confidence interval; DB ETN = Double-blind etanercept; ESR = Erythrocyte sedimentation rate; ITT = Intent-to-treat; LOCF = Last observation carried forward; OL ETN = Open-label etanercept; SD = Standard deviation; SE = Standard error.
a. ANCOVA model on change from Baseline ASDAS ESR Score fitting Baseline ASDAS ESR Score as a covariate, plus treatment as a factor.

Table 23. Description of ASDAS ESR - Absolute and Change From Baseline Values (OC) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	37	37		
	Mean	3.3	3.1		
	SD	0.89	0.77		
	Median	3.1	3.1		
	Min	2	2		
	Max	5	5		
Week 4	N	31	35	28	31
	Mean	2.6	3.1	-0.8	-0.2
	SD	0.93	0.97	0.78	0.53
	Median	2.7	3	-0.8	-0.2
	Min	1	1	-2	-1
	Max	4	6	1	1
Week 8	N	33	35	29	31
	Mean	2.1	2.8	-1.1	-0.4
	SD	1.09	1.01	1.2	0.83
	Median	1.8	3	-0.7	-0.3
	Min	0	1	-4	-3
	Max	4	5	0	1
Week 12	N	27	35	25	32
	Mean	2.2	2	-1	-1
	SD	1.02	0.92	1.1	1.01
	Median	2	2	-0.7	-0.8
	Min	1	0	-4	-4
	Max	4	4	0	0
Week 16	N	26	30	23	26
	Mean	2	1.7	-1.3	-1.3
	SD	0.95	0.93	0.79	1.21
	Median	1.9	1.7	-1.5	-1
	Min	1	0	-3	-4
	Max	4	4	0	0

N is the number of subjects with available assessments at the corresponding visit.
Means and Medians have been determined within a subject prior to summarizing across subjects. Baseline is defined to be the latest non-missing value from a range of pre-treatment visits. The minimum and maximum values have been determined from all values recorded.
Unplanned readings have been excluded from the presentation.
ASDAS = Ankylosing Spondylitis Disease Activity Score; DB ETN = Double-blind etanercept; ESR = Erythrocyte sedimentation rate; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; OC = Observed case; OL ETN = Open-label etanercept; SD = Standard deviation.

Extra-Spinal and Extra-Articular Involvement:

No statistical significant differences were detected between subjects in the DB ETN 50 mg to OL ETN 50 mg group and placebo to OL ETN 50 mg group for acute anterior uveitis and psoriasis at Weeks 4, 8, 12 and 16. IBD was not reported in either treatment group.

For the ITT population, the summary of proportions of extra spinal and extra articular involvement (acute anterior uveitis, IBD and psoriasis) at Weeks 4, 8, 12 and 16 is provided in Table 24 (with OC).

Table 24. Extra-Spinal and Extra-Articular Involvement - Proportions (OC) ITT Population - Acute Anterior Uveitis

Week	DB ETN 50 mg to OL ETN 50 mg n/N (%)	Placebo to OL ETN 50 mg n/N (%)	Odds Ratio[a]		
			Estimate	(95% CI)	p-Value
Week 4	4/40 (10.00%)	1/46 (2.17%)	4.97	(0.52, 47.51)	0.1638
Week 8	2/37 (5.41%)	1/42 (2.38%)	2.37	(0.20, 27.49)	0.4906
Week 12	2/35 (5.71%)	1/42 (2.38%)	2.50	(0.22, 29.06)	0.4640
Week 16	1/28 (3.57%)	1/36 (2.78%)	1.30	(0.08, 21.84)	0.8538

N is the number of subjects with non-missing assessment at corresponding visit.
n is the number of subjects with disease occurrence at corresponding visit.
CI = Confidence interval; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; OC = Observed case; OL ETN = Open-label etanercept.

a. Logistic regression with Baseline Morning Stiffness Score and treatment group included as covariates.

C-Reactive Protein (CRP):

For the DB ETN 50 mg to OL ETN 50 mg group, the median change from Baseline at Week 4, 8, 12 and 16 was -0.2, -0.3, -0.4 and -0.6 mg/dL , respectively, showing an improvement over time. No apparent change from Baseline was observed for the Placebo to OL ETN 50 mg group up to Week 8; a small change was observed at Weeks 12 and 16 (the median was -0.2 mg/dL for both) when switching to ETN treatment, showing slight improvement.

For the ITT population, the summary of absolute values and the change from Baseline for CRP at Weeks 4, 8, 12 and 16 is provided in Table 25.

Table 25. Description of CRP (mg/dL) - Absolute and Change From Baseline Values (OC) ITT Population

Week		Absolute Values		Change From Baseline	
		DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
Baseline	N	42	48		
	Mean	1.0	0.9		
	SD	1.34	1.36		
	Median	0.6	0.4		
	Min	0	0		
	Max	6	7		
Week 4	N	39	46	39	46
	Mean	0.3	0.8	-0.8	-0.2
	SD	0.31	1.04	1.35	0.67
	Median	0.2	0.5	-0.2	0.0
	Min	0	0	-5	-2
	Max	2	5	1	1
Week 8	N	38	44	38	44
	Mean	0.3	0.6	-0.7	-0.3
	SD	0.54	0.76	1.42	1.43
	Median	0.1	0.3	-0.3	-0.1
	Min	0	0	-6	-7
	Max	3	4	2	4
Week 12	N	35	42	35	42
	Mean	0.2	0.4	-0.9	-0.6
	SD	0.14	0.91	1.38	1.68
	Median	0.1	0.1	-0.4	-0.2
	Min	0	0	-6	-7
	Max	1	6	0	6
Week 16	N	28	38	28	38
	Mean	0.2	0.2	-0.9	-0.8
	SD	0.17	0.16	1.40	1.45
	Median	0.1	0.1	-0.6	-0.2
	Min	0	0	-6	-7
	Max	1	1	0	1

N is the number of subjects with available assessments at the corresponding visit.
Means and Medians have been determined within a subject prior to summarizing across subjects. Baseline is defined to be the latest non-missing value from a range of pre-treatment visits. The minimum and maximum values have been determined from all values recorded.
Unplanned readings have been excluded from the presentation.
CRP = C-reactive protein; DB ETN = Double-blind etanercept; ITT = Intent-to-treat; Max = Maximum; Min = Minimum; N = Number of subjects; OC = Observed case; OL ETN = Open-label etanercept; SD = Standard deviation.

Health Outcomes Assessment Endpoint:

Ankylosing Spondylitis Work Instability Scale (AS WIS):

There was no difference between treatment groups in the change from Baseline to Week 8 in AS WIS score (p = 0.9919). The change from Baseline to Week 16 in AS WIS score for ETN only was statistically significant (adjusted mean change from Baseline -3.00 [95%CI: -5.67, -0.33], p = 0.0301).

Safety Results:

All causality treatment-emergent AEs (TEAEs) by preferred term that occurred in ≥2 subjects in either treatment group according to decreasing frequency for the DB ETN 50 mg to OL ETN 50 mg group are displayed in Table 26.

Table 26. All Causality Treatment Emergent Adverse Events by Preferred Term (Occurring in ≥2 Subjects in Either Treatment Group) According to Descending Frequency in the DB ETN 50 mg to OL ETN 50 mg Group

	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
DB Treatment Period	**N=42**	**N=48**
Rhinitis	5 (11.9%)	2 (4.2%)
Asthenia	3 (7.1%)	3 (6.3%)
Hypercholesterolaemia	3 (7.1%)	0
Injection site hypersensitivity	3 (7.1%)	0
Injection site reaction	3 (7.1%)	0
Headache	2 (4.8%)	1 (2.1%)
Injection site erythema	2 (4.8%)	0
Rash	2 (4.8%)	0
Abdominal pain	1 (2.4%)	3 (6.3%)
Hypertension	1 (2.4%)	2 (4.2%)
Injection site pruritus	1 (2.4%)	2 (4.2%)
Alopecia	0	2 (4.2%)
Diarrhoea	0	2 (4.2%)
Pruritus	0	2 (4.2%)
OL Treatment Period	**N=31**	**N=33**
Headache	2 (6.5%)	2 (6.1%)
Injection site pruritus	2 (6.5%)	0
Migraine	2 (6.5%)	0
Oral herpes	2 (6.5%)	0
Injection site erythema	0	4 (12.1%)
Injection site reaction	0	3 (9.1%)
Nasopharyngitis	0	2 (6.1%)
Pharyngitis	0	2 (6.1%)
Escape Arm	**N=6**	**N=11**
Nausea	0	2 (18.2%)
ALT increased	0	2 (18.2%)

Adverse events/serious adverse events are not separated out.
Includes data up to 15 days after last dose of study drug.
Except for the number of adverse events, subjects are counted only once per treatment in each row.
ALT = Alanine aminotransferase; DB = Double-blind; ETN = Etanercept; OL = Open-label; N = subjects evaluable for adverse events.

During the DB treatment period, more subjects in the DB ETN 50 mg to OL ETN 50 mg group experienced all causality TEAEs and treatment related TEAEs (34 [81%] subjects and 18 [43%] subjects, respectively) than in the placebo to OL ETN 50 mg group (26 [54%] subjects and 12 [25%] subjects, respectively).

During the OL treatment period, the incidence of all causality TEAEs and treatment related TEAEs was lower or similar in the DB ETN 50 mg to OL ETN 50 mg group (12 [39%] subjects and 7 [23%] subjects, respectively) with the respect to the placebo to OL ETN 50 mg group (17 [52%] subjects and 9 [27%] subjects, respectively).

In the Escape Arm, all subjects of the DB ETN 50 mg to OL ETN 50 mg group and about 82% of subjects who were in the placebo to OL ETN 50 mg group reported all causality TEAEs for the DB treatment period phase. Treatment related TEAEs were reported for

about 17% subjects in the DB ETN 50 mg to OL ETN 50 mg group and about 36% in the placebo to OL ETN 50 mg group.

The most common reported all-causality TEAEs reported during the DB treatment period were rhinitis, asthenia, hypercholesterolaemia, injection site hypersensitivity and injection site reaction in the DB ETN 50 mg to OL ETN 50 mg group, and asthenia and abdominal pain in the placebo to OL ETN 50 mg group. During the OL treatment period, the most common reported all-causality TEAEs reported in the DB ETN 50 mg to OL ETN 50 mg group were headache, injection site pruritus, migraine and oral herpes, and in the placebo to OL ETN 50 mg group injection site erythema, injection site reaction, headache, nasopharyngitis and pharyngitis. In the Escape Arm, the most common reported all causality TEAE reported was alanine aminotransferase (ALT) increased. These results are in keeping with the label.

Treatment related TEAEs by preferred term that occurred in ≥2 subjects in either treatment group according to decreasing frequency for the DB ETN 50 mg to OL ETN 50 mg group are displayed in Table 27.

Table 27. Treatment Related Treatment Emergent Adverse Events by Preferred Term (Occurring in ≥2 Subjects in Either Treatment Group) According to Descending Frequency in the DB ETN 50 mg to OL ETN 50 mg Group

	DB ETN 50 mg to OL ETN 50 mg	Placebo to OL ETN 50 mg
DB Treatment Period	**N=42**	**N=48**
Asthenia	3 (7.1%)	2 (4.2%)
Injection site hypersensitivity	3 (7.1%)	0
Injection site erythema	2 (4.8%)	0
Injection site reaction	2 (4.8%)	0
Rash	2 (4.8%)	0
Rhinitis	2 (4.8%)	0
Alopecia	0	2 (4.2%)
OL Treatment Period	**N=31**	**N=33**
Injection site pruritus	2 (6.5%)	0
Migraine	2 (6.5%)	0
Injection site erythema	0	4 (12.1%)
Injection site reaction	0	2 (6.1%)
Escape Arm	**N=6**	**N=11**
Nausea	0	2 (18.2%)

Adverse events/serious adverse events are not separated out.
Includes data up to 15 days after last dose of study drug.
Subjects are counted only once per treatment in each row.
DB = Double-blind; ETN = Etanercept; OL = Open-label; N = Subjects evaluable for adverse events.

The most common treatment related TEAEs by preferred term during the DB treatment period in the DB ETN 50 mg to OL ETN 50 mg group included asthenia and injection site hypersensitivity (3 [7%] subjects each) and injection site erythema, injection site reaction, rash and rhinitis (2 [5%] subjects each). In the placebo to OL ETN 50 mg group, the most common treatment related TEAEs were asthenia and alopecia (2 [4%] subjects each). The most common treatment related TEAEs by preferred term during the OL treatment period in

the DB ETN 50 mg to OL ETN 50 mg group included injection site pruritus, migraine, (2 [7%] subjects each), and in the placebo to OL ETN 50 mg group included injection site erythema (4 [12%] subjects) and injection site reaction (2 [6%] subjects).

An overview of subjects with SAEs is presented in Table 28.

Table 28. Subjects With Serious Adverse Events

Treatment Group	Sex/Age/Race	AE(s) by Preferred Term	Study Start Day[a]/ Study Stop Date[a]	Severity	Related to study drug?	Action taken	Outcome
DB Treatment Period							
DB ETN 50 mg to OL ETN 50 mg	Male/32/White	Duodenitis[b]	33/71	Severe	N	Permanent discontinuation; concomitant medication	Resolved
Placebo to OL ETN 50 mg	Male/48/White	Road traffic accident[b]	27/27	Moderate	N	None; concomitant medication	Resolved
	Male/33/White	Chest pain[b]	9/9	Severe	N	None; concomitant medication	Resolved
OL Treatment Period							
DB ETN 50 mg to OL ETN 50 mg	Male/25/White	Chole-cystitis	114/148	Moderate	Y	Permanent discontinuation; concomitant medication	Resolved
Placebo to OL ETN 50 mg	Male/48/White	Cyst removal[b]	113/169	Moderate	N	Temporarily discontinued; concomitant medication	Resolved
	Male/33/White	Renal colic	141/142	Severe	N	None; concomitant medication	Resolved
	Female/28/White	Nodal arrhythmia	133/134	Severe	Y	None; cardiac surgery	Resolved

AE = Adverse events; DB = Double-blind; ETN = Etanercept; N = No; OL = Open-label; Y = Yes.
a. Day relative to start of study treatment. First day of each treatment period = Day 1.
b. Treatment-emergent.

During the DB treatment period, the incidence of all causality SAEs was low: 1 subject in the DB ETN 50 mg to OL ETN 50 mg group (duodenitis) and 2 subjects in the placebo to OL ETN 50 mg group (road traffic accident and chest pain). The SAE of duodenitis led to permanent discontinuation from study drug.

During the OL treatment period, the incidence of all causality SAEs was low (no event in the DB ETN 50 mg to OL ETN 50 mg group; 1 subject in the placebo to OL ETN 50 mg group underwent cyst removal which caused permanent discontinuation of the study drug).

No treatment related SAEs in both treatment groups were reported in either treatment period.

Post treatment, an all causality SAE was reported for 1 subject of the placebo to OL ETN 50 mg group (renal colic). Treatment related SAEs were reported for 1 subject of the DB ETN 50 mg to OL ETN 50 mg group (cholecystitis) and for 1 subject of the placebo to OL ETN 50 mg group (nodal arrhythmia).

In the Escape Arm, no event regarding all causality or treatment related AEs was considered serious.

Permanent discontinuations, dose reductions and temporary discontinuations due to all causality TEAEs or treatment related TEAEs were low in both treatment groups. An overview of subjects who discontinued permanently due to AEs is presented in Table 29. AEs considered to be related to study drug that led to permanent discontinuation was reported for 1 subject (condition aggravated) in the DB ETN 50 mg to OL ETN 50 mg group during the DB treatment period, and for 1 subject (injection site erythema) in the placebo to OL ETN 50 mg group during the OL treatment period.

Table 29. Subjects Who Discontinued Study Treatment Permanently Due to Adverse Events

Treatment Group	Sex/Age/Race	AE(s) by Preferred Term	Study start day+/Study stop date+	Severity	Related to Study Drug?	Action taken	Outcome
DB Treatment Period							
DB ETN 50 mg to OL ETN 50 mg	Female/35/White	Injection site reaction*	8/24	Moderate	N	Permanent discontinuation; concomitant medication	Resolved
	Male/37/White	Condition aggravated*	29/>29	Moderate	Y	Permanent discontinuation	Still present
Placebo to OL ETN 50 mg	Male/30/White	Gastro-enteritis	22/33	Mild	N	Permanent discontinuation	Resolved
OL Treatment Period							
DB ETN 50 mg to OL ETN 50 mg	Male/32/White	Duodenitis*	33/71	Severe	N	Permanent discontinuation; concomitant medication	Resolved
Placebo to OL ETN 50 mg	Male/45/White	Naso-pharyngitis*	84/91	Mild	N	Permanent discontinuation; concomitant medication	Resolved
	Female/32/White	Injection site erythema*	89/98	Mild	Y	Permanent discontinuation; concomitant medication	Resolved
Escape Arm							
DB ETN 50 mg to OL ETN 50 mg	Male/28/White	Alanine amino-transferase increased*	1/>47	Mild	N	Permanent discontinuation; hepatic echography and abdominal scanner	Still present

* Treatment-emergent.
+ Day relative to start of study treatment. First day of each treatment period = Day 1.
AE = Adverse events; DB = Double-blind; ETN = Etanercept; N = No; OL = Open-label; Y = Yes.

Only few subjects reported hematology (2), renal function (1), lipid (11), electrolytes (5), other chemistry (2) abnormalities. Immunology abnormalities were reported for elevation of C-reactive protein (CRP); urinalysis abnormalities were reported for elevation of urine specific gravity and for urine red blood cells.

In general, with the exception of the above mentioned results, no clinically significant hematology, renal function, lipid, electrolytes, other chemistry, immunology, or urinalysis abnormalities were reported during the study.

During the DB treatment period, liver function test abnormalities (without regard to baseline abnormality) were reported in the DB ETN 50 mg to OL ETN 50 mg group for 1 subject (ALT increased >3.0 x upper limit of normal [ULN]), and in the placebo to OL ETN 50 mg group, for 2 subjects (ALT increased >3.0 x ULN) and for 1 subject (AST increased >3.0 x ULN). These events were assessed as AEs. In addition, an AESI of hepatocellular injury was reported for 1 subject (DB ETN 50 mg to OL ETN 50 mg group); ALT values were also reported as increased. No liver function test abnormalities (without regard to baseline abnormality) were reported during the OL treatment period. No cases fulfilled Hy's Law.

One subject reported a non serious AE of increased BP at Baseline. In general, with the exception of this AE, no clinically significant vital signs abnormalities were reported.

No clinically relevant observations regarding physical examinations were reported.

No deaths were reported during the study.

CONCLUSIONS:

- The primary objective of this study was met. A statistically significant benefit of ETN was observed on the primary endpoint, the change from Baseline NSAID ASAS Score at Week 8.

- For most of the secondary endpoints, a statistically significant benefit of ETN over placebo was observed.

- Safety data were as expected.