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

PROTOCOL NO: 0881K1-4500 (B1801016)

PROTOCOL TITLE: Dose Reduction or Discontinuation of Etanercept in Methotrexate-Treated Rheumatoid Arthritis Subjects Who Have Achieved a Stable Low Disease Activity-State (DOSERA)

Study Centers: A total of 16 centers took part in the study and randomized subjects; 2 in Denmark, 1 in Iceland, 2 in Finland, 3 in Norway, 5 in Sweden and 3 in Hungary.

Study Initiation Date and Final Completion Date: 02 September 2009 to 20 June 2012

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

To compare the effect on disease activity of the combination of etanercept (ETN) 50 mg once a week (QW) plus methotrexate (MTX) to placebo plus MTX over 48 weeks in rheumatoid arthritis (RA) subjects who at study start were in remission or low disease activity (LDA) state with combination therapy with ETN 50 mg weekly plus MTX.

Secondary Objectives:

- To compare the effect on disease activity of the combination of ETN 25 mg QW plus MTX to:
    - combination of ETN 50 mg QW plus MTX
    - placebo plus MTX

over 48 weeks in RA subjects who at study start were in remission or LDA state with combination therapy with ETN 50 mg weekly plus MTX.

- To compare the change in modified Total Sharp Score (mTSS) over 48 weeks among the treatment groups.

METHODS

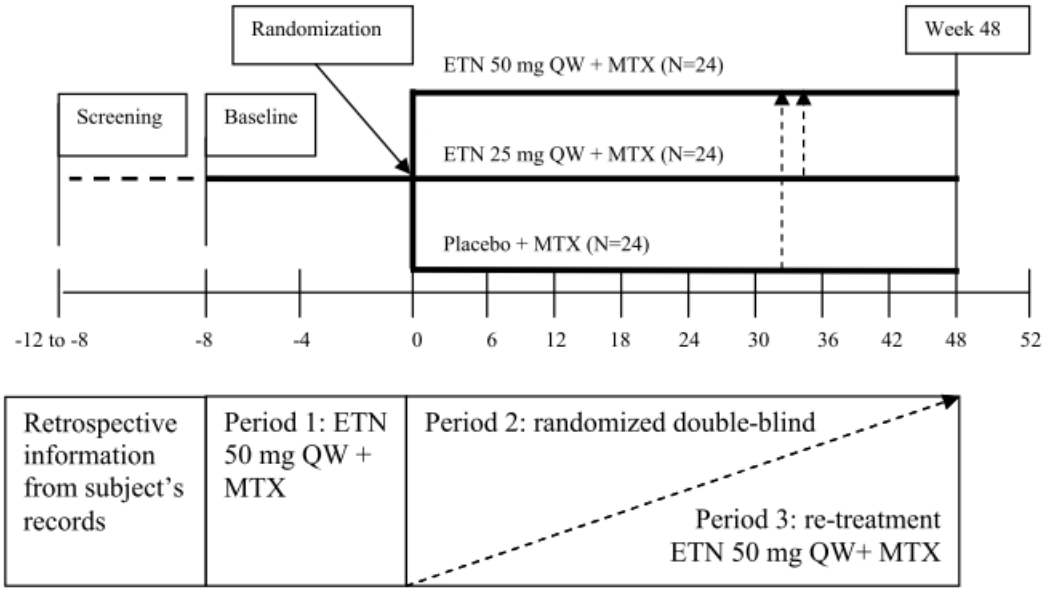
Study Design: This was a 64-week, Phase 4, multicenter, parallel group, placebo-controlled, randomized, double blind, prospective, and outpatient study of ETN in MTX-treated RA subjects who had achieved remission or a stable LDA-state. The Study included a screening period of up to 4 weeks, an 8-week open-label period (Period 1), a 48-week or until failure double-blind randomized period (Period 2), an open-label period from failure to study end (Period 3) and a 4-week follow-up period. The study design is presented in Figure 1.

During Period 1 subjects were followed for 8 weeks without change in medication to ensure consistent remission or LDA state. However, subjects who had been treated with ETN 25 mg biweekly were switched to 50 mg QW at the baseline visit.

Subjects completing Period 1 and who maintained a Disease Activity Score based on a 28-joint count (DAS28) ≤3.2 were randomly assigned to one of the 3 treatment groups in Period 2 in a 1:1:1 ratio. Subjects were stratified by DAS28 value (<2.6; 2.6-3.2) during the entire year up to and including randomization visit. Subjects withdrawn from the study were not replaced, regardless of the reason for withdrawal. Subjects continued in Period 2 from randomization (Week 0) to failure, Week 48 or early withdrawal.

Progression from Period 2 to Period 3 was dependent on the subject meeting treatment failure criteria regarding the DAS28 value and/or disease progression. Period 2 and Period 3 had a combined duration of 48 weeks, such that subjects meeting the entry criteria for Period 3 during any given week of Period 2 would then spend the remainder of the 48 week timeframe (or until withdrawal) in Period 3. Subjects that never met the treatment failure criteria during Period 2, remained in Period 2 for the full 48 week period (or until withdrawal) and never entered Period 3. The study flow chart is summarized in Table 1.

Figure 1 Study Design



ETN = etanercept; MTX = methotrexate; N = number of subjects, QW = once a week.

Table 1. Study Flow Chart

Study Week[a]	**-12 to -8**[b]	**-8**	**-4**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**Final/ 48**		**50**
Study Interval	**Screening**	**Baseline**	**Open-Label Period**	**Randomization**	**Double-Blind Randomized Period**								**Extra Visit**[c]	**F-up**[d]
Visit ID (For Sponsor Use Only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**[e]		**13**
Informed consent	X													
Inclusion, exclusion criteria	X	X[f]	X	X										
Randomization				X										
Demographics	X													
Medical history	X													
Prior medications	X													
Tobacco use		X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X			X								X		
Vital signs	X	X[f]		X	X	X	X	X	X	X	X	X	X	
Height	X													
Weight	X											X		
Joint assessment[g,h]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	
ECG		X												
Physician global assessment[g]		X	X	X	X	X	X	X	X	X	X	X	X[i]	
Subject global assessment		X	X	X	X	X	X	X	X	X	X	X	X[i]	
Subject morning stiffness		X	X	X	X	X	X	X	X	X	X	X	X[i]	
Subject general health VAS[h]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	
Subject pain VAS		X		X	X	X	X	X	X	X	X	X	X[i]	
HAQ		X		X	X	X	X	X	X	X	X	X	X[i]	
WPAI-RA		X		X	X	X	X	X	X	X	X	X	X[i]	
PASS		X		X	X	X	X	X	X	X	X	X	X[i]	
EQ-5D		X		X		X		X		X		X	X[i]	
FACIT Fatigue scale[j]		X		X		X		X		X		X	X[i]	
DAS28 calculation	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	
CDAI		X	X	X	X	X	X	X	X	X	X	X	X	
SDAI		X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Study Flow Chart

Study Week[a]	**-12 to -8**[b]	**-8**	**-4**	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**Final/ 48**		**50**
Study Interval	**Screening**	**Baseline**	**Open-Label Period**	**Randomization**	**Double-Blind Randomized Period**								**Extra Visit**[c]	**F-up**[d]
Visit ID (For Sponsor Use Only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**[e]		**13**
Urinalysis, chemistry and hematology	X	X[f]		X		X		X		X		X	X	
CRP, ESR[h]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	
Rheumatoid factor	X													
Serum biomarkers[k]				X		X								
Pregnancy test, urine[l]		X												
Hand, wrist, forefoot radiographs[m]				X								X		
Hand and wrist MRI, dominant hand[n]				X		X								
Return investigational product/ Drug accountability			X	X	X	X	X	X	X	X	X	X	X	
Dispense investigational product		X	X	X	X	X	X	X	X	X	X		X[i]	
Dispense subject investigational product diary		X	X	X	X	X	X	X	X	X	X		X[i]	
Collect and review subject investigational product diary			X	X	X	X	X	X	X	X	X	X	X[i]	
Adverse events[o]		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Study Flow Chart

Study Week[a]	-12 to -8[b]	-8	-4	0	6	12	18	24	30	36	42	Final/ 48		50
Study Interval	Screening	Baseline	Open-Label Period	Randomization	Double-Blind Randomized Period								Extra Visit[c]	F-up[d]
Visit ID (For Sponsor Use Only)	1	2	3	4	5	6	7	8	9	10	11	12[e]		13

CCP = anti-cyclic citrullinated peptide; CDAI = Clinical Disease Activity Index; COMP = cartilage oligomeric matrix protein; CRP = C- reactive protein; DAS28 = Disease Activity Score based on a 28-joint count; ECG = electrocardiogram; EQ-5D = EuroQoL-5 Dimensions; ESR = erythrocyte sedimentation rate; F-up = follow up; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; ID = identification; MRI = Magnetic Resonance Imaging; PASS = Patient Acceptable Symptom State; SDAI = Simplified Disease Activity Index; VAS = visual analog scale; WPAI-RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. The visit window for Visits 3 through 12 was ± 5 days.
b. Screening and baseline evaluation could be done during the same visit, if all necessary data including laboratory tests for inclusion were available.
c. Extra visit to examine the subject, record signs and symptoms and decide on continuation of the blinded phase (Period 2) or transfer the subject into open-label phase (Period 3).
d. There was a follow-up telephone call to assess new and ongoing adverse events at:
   28 days +5 days after Week 0 (Visit 4) if the subject was not randomized; or
   28 days +5 days after early discontinuation, if the subject discontinued early from the study; or
   28 days +5 days after Week 48 (Visit 12), if the subject completed the study.
e. For early termination, final visit procedures were performed at the time of withdrawal or discontinuation.
f. The procedure did not need to be repeated at the baseline visit, if it was completed at the screening visit ≤5 days before baseline.
g. It was recommended that the same qualified personnel completed these assessments at each visit.
h. These procedures constituted the DAS28 exam and were done at all visits.
i. Procedure had not to be conducted, if subject continued the blinded phase (Period 2).
j. Not to be assessed in Icelandic subjects.
k. Serum biomarkers: sensitive serum CRP, anti-CCP, COMP, and survivin. The subject had to be fasting and the samples taken before 10 am, if possible.
l. For women of childbearing potential only. Pregnancy test may have been repeated after baseline visit at the discretion of the investigator.
m. For subjects who withdrew prior to Week 48, the investigator attempted to obtain X-rays on the subjects at the Week 48 time point (with a 1 month window).
n. For subjects who withdrew prior to Week 12, the investigator attempted to obtain MRI on the subjects at the Week 12 time point (±5 days).
o. Adverse events were reported from the signing of the informed consent form.

Number of Subjects (Planned and Analyzed): Approximately 105 subjects were screened of which 72 subjects were randomized at the end of Period 1 with 24 subjects in each of the 3 treatment groups. A total of 106 subjects were screened, of which 91 subjects received at least 1 dose of ETN in Period 1 and were included in the safety subset Period 1. A total of 33 subjects were screened but were not randomized, mostly due to high DAS28 level (>3.2). A total of 73 subjects entered Period 2 and were randomized (23 subjects in the ETN 50 mg + MTX group, 27 subjects in the ETN 25 mg + MTX group, and 23 subjects in the placebo + MTX group). All 73 randomized subjects (4 in Denmark, 8 in Finland, 12 in Hungary, 6 in Iceland, 7 in Norway and 36 in Sweden) were included in the modified intent-to-treat (mITT) set and the safety subset Period 2. The safety subset Period 3 included 43 randomized subjects with at least 1 dose of ETN in Period 3.

Diagnosis and Main Criteria for Inclusion: Male and female subjects at least 18 years old, with a diagnosis of RA and functional status of class I, II, or III based on the American College of Rheumatology Revised Criteria for RA, with DAS28≤3.2, receiving treatment with subcutaneous (SC) ETN, either 25 mg BW or 50 mg QW, for a minimum of 14 months at baseline, receiving oral, SC or intramuscular (IM) MTX, 7.5 mg/week to 25 mg/week and at a stable dose for a minimum of 4 months at baseline.

Study Treatment: The investigational product was ETN SC injections. ETN was supplied in vials as a sterile lyophilized powder containing 25 or 50 mg of ETN. Oral, SC or IM MTX was administered at a dose of 7.5 mg to 25 mg weekly as a single dose or in divided doses each week.

In Period 1, subjects received ETN 50 mg QW. In Period 2, subjects were randomly assigned to 1 of 3 treatment groups:

- ETN 50 mg SC QW + MTX
- ETN 25 mg SC QW + MTX
- ETN placebo SC QW + MTX

In Period 3, subjects were re-treated with open-label ETN 50 mg SC QW + MTX.

Efficacy Endpoints:

Primary Endpoint: Proportion of subjects who were non-failures at Week 48. These subjects were still in Period 2 at study end, which meant they had not fulfilled predefined failure criteria during the study.

Secondary Endpoints: In the 3 treatment arms:

- Time from randomization to failure
- Proportion of subjects in remission or LDA state at each visit
- Proportion of time subjects were in remission or LDA state
- Change in DAS28 at each visit

- Change in tender and swollen joints at each visit
- Change in physician global assessments, subject global assessments, subject global health Visual Analog Scale (VAS), subject pain VAS and morning stiffness at each visit
- Changes in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at each visit
- Change in mTSS at Week 48
- Correlation between clinical assessment, serum biomarkers, Magnetic Resonance Imaging (MRI) (at randomization and Week 12) and X-ray findings at randomization and whether individuals have had treatment failure or not.

Safety Evaluations: Adverse events (AEs) (serious and nonserious), clinically significant abnormal laboratory tests (recorded as AEs), vital signs (heart rate, blood pressure), and physical examination.

Statistical Methods:

Full Analysis Set*:* The primary efficacy analysis set was the mITT set defined as all randomized subjects who received at least 1 dose of investigational product (ETN or placebo) after randomization and who had at least 1 available evaluation after the first administration of investigational product after randomization. Subjects were analyzed according to the treatment allocated by randomization.

Safety Analysis Set: All subjects who received at least 1 dose of investigational product (ETN or placebo) were included in the evaluation for safety. To analyze safety separately for the 3 periods, 3 subsets of safety set were defined, 1 for each period:

- Safety Set (Run-in Open Label) Period 1: subjects with at least 1 dose of ETN in Period 1
- Safety Set (Double-blind Randomized) Period 2: randomized subjects with at least 1 dose of ETN or placebo in Period 2
- Safety Set (Re-treatment Open Label) Period 3: randomized subjects with at least 1 dose of ETN in Period 3

In Period 2, subjects were analyzed according to the treatment actually received.

The primary endpoint ie, non-failures at Week 48. Non-failure was defined as:

- Calculated DAS28 ≤3.2 at all visits or if calculated DAS28 >3.2, the increase from randomization was: <0.6 at all visits or ≥0.6 but <1.2 on no more than 1 consecutive visit

- And no progression of disease as determined by the Investigator and/or subject at all visits

The proportion of non-failure subjects at a particular endpoint was analyzed using a Generalized Estimating Equations (GEE) model, using a logit link, a binomial distribution and an auto-regressive correlation structure. This analysis was performed on last observation carried forward (LOCF) data. Pairwise comparisons between groups at each time point were obtained from the above model using appropriate contrasts.

Two sensitivity analyses were performed, the first considering only LOCF data at Week 48 analyzed with a logistic regression model and the second using the same model as the main analysis but with subjects who discontinued prematurely considered as failures (non-responder imputation).

The secondary analyses were performed on the mITT set overall and according to the randomization group.

The time from randomization to failure in Period 2 and the time from failure to LDA and remission during Period 3 were analyzed using a Cox Proportional Hazards model and Kaplan Meier estimates.

Due to convergence issues and sparsity of data, the secondary endpoint of proportion of subjects in LDA/remission had not been analyzed with a GEE model as planned; separate logistic regression models were run at each time point (instead of a single repeated measures model).

The change from randomization of all parameters were analysed using a mixed model repeated measures.

The proportion of subjects in treatment failure over 48 weeks was first analysed using univariate logistic regressions with each of the predictors as a fixed factor. Predictive variables significant at a threshold of 10% in the univariate analysis were entered in a multivariate model that used a backward selection of significant predictive variables and significant interactions with randomization group: all probability values ≤0.05 were considered statistically significant.

RESULTS:

Subject Disposition and Demography: Subject disposition is summarized in Table 2. Of 106 subjects screened, 73 entered Period 2. A total of 33 subjects were screened but not randomized, mostly due to high DAS28 level. A total of 7 subjects (10%) discontinued the study prematurely. Five subjects discontinued prematurely during Period 2 (3 subjects did not wish to continue, 1 subject withdrew due to a serious adverse event [SAE], and 1 subject withdrew prematurely due to other reasons). Two subjects discontinued prematurely during Period 3 (1 due to protocol violation and 1 for other reasons).

Table 2. Subject Disposition

Number of Subjects	ETN 50 mg + MTX	ETN 25 mg + MTX	Placebo + MTX	Total
Screened				106
Received at least one dose of ETN in Period 1				91
Total randomized (Period 2)	23	27	23	73
mITT Set	23	27	23	73
Re-treatment Period 3				43

ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate.

The subject disposition by visit is presented in Table 3. Of the 23 subjects randomized in the ETN 50 mg + MTX group, 15 (65%) were still in Period 2 at Week 24 and 13 (57%) at Week 42. Out of the 27 subjects randomized in the ETN 25 mg + MTX group, 16 (64%) were still in Period 2 at Week 24 and 12 (48%) at Week 42. Out of the 23 subjects randomized in the Placebo + MTX group, only 3 (13%) were still in Period 2 from Week 18 and 2 (9%) from Week 36.

Table 3. Subject Disposition by Visit-Periods 2 and 3-mITT Set

	ETN 50 mg + MTX (N=23)		ETN 25 mg + MTX (N=27)		Placebo + MTX (N=23)	
	Period 2	Period 3	Period 2	Period 3	Period 2	Period 3
Randomization	23		27 1[a]		23	
Week 6	22	1	26	0 1[a]	15 1[a]	8
Week 12	19	4	22	3	5	17 1[a]
Week 18	17	6	19	6	3	18
Week 24	15	8	16	9	3	18
Week 30	15	8	15	10	3	18
Week 36	13	10	14 1[a]	11	2	19
Week 42	13 2[a]	10	12	12	2	19
Week 48/ Early termination	13	10	14	13	3	20

ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate; N = total number of subjects.
a. Premature withdrawal.

The subject's age ranged from 24 to 77 years and mean age at screening was 54 years in the ETN 50 mg + MTX, 60 years in the ETN 25 mg + MTX group, and 56 years in the placebo + MTX group. All subjects except 1 were Caucasian with similar gender distribution between randomized groups. Globally, 30% of subjects were male and 70% were female, of which 25% were of childbearing potential.

A summary of demographic and baseline characteristics is presented in Table 4.

Table 4. Demographic and Baseline Characteristics-mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Age (years)				
Mean (SD)	53.8 (12.1)	59.6 (9.2)	56.1 (11.5)	56.7 (11.0)
Median (Min; Max)	54.6 (32.0; 73.0)	59.7 (39.1; 76.7)	57.2 (23.8; 75.1)	58.7 (23.8; 76.7)
Gender, n (%)				
Male	6 (26%)	9 (33%)	7 (30%)	22 (30%)
Female	17 (74%)	18 (67%)	16 (70%)	51 (70%)
of childbearing potential[a]	7 (41%)	3 (17%)	3 (19%)	13 (25%)
Race, n (%)				
White/ Caucasian	22 (96%)	27 (100%)	23 (100%)	72 (99%)
Other	1 (4%)	-	-	1 (1%)
Tobacco smoker, n (%)				
Never	11 (48%)	10 (37%)	15 (65%)	36 (49%)
Current	2 (9%)	7 (26%)	2 (9%)	11 (15%)
Former	10 (43%)	10 (37%)	6 (26%)	26 (36%)

ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate; Min = minimum; Max = maximum; N = total number of subjects; n = number of subjects in the specified group; SD = standard deviation.
a. Denominator for calculating the percentage is the number of females.

Efficacy Results:

Primary Endpoint Result: Of 73 randomized subjects, 27 (37%) were considered as non-failures at Week 48: 52% in the ETN 50 mg + MTX group, 44% in the ETN 25 mg + MTX group compared to 13% in the placebo + MTX group. The results are summarized in Table 5.

Table 5. Proportion of Non-Failures Based on Calculated DAS28 and Disease Progression as Determined by the Investigator or the Subject-Observed Data-Endpoint-mITT Set

Week 48/LOCF	ETN 50 mg + MTX	ETN 25 mg + MTX	Placebo + MTX	Total
n	23	27	23	73
Non-failure	12 (52%)	12 (44%)	3 (13%)	27 (37%)
Failure	11 (48%)	15 (56%)	20 (87%)	46 (63%)

LOCF was applied to the time points where data were missing at subsequent visits.
DAS28 = Disease Activity Score based on a 28-joint count; ETN = etanercept; LOCF = last observation carried forward; mITT = modified intent-to-treat; MTX = methotrexate; n = number of subjects in the specified group.

The proportion of non-failures at Week 48 for the group ETN 50 mg + MTX was significantly higher compared to the group receiving placebo + MTX, with an estimated odds ratio (95% CI) of 7.2 (1.7; 29.8) (p=0.007). There was also a significant difference for pairwise comparison of ETN 25 mg + MTX and placebo + MTX (p=0.044). There was no statistically significant difference in the proportion of non-failures at Week 48 between the 2 active groups (ETN 50 mg + MTX and ETN 25 mg + MTX). The proportion of non-failures at each time point is summarized in Table 6.

Table 6. Proportion of Non-Failures-Estimated Odds Ratios-mITT Set

Comparison	Estimate	Odds Ratio (95% CI)	p-value (G)
Week 6			
ETN 50 mg + MTX / Placebo + MTX	9.0	(1.7; 46.8)	0.009
ETN 50 mg + MTX / ETN 25 mg + MTX	1.2	(0.2; 6.1)	0.830
ETN 25 mg + MTX / Placebo + MTX	7.6	(1.9; 30.1)	0.004
Week 12			
ETN 50 mg + MTX / Placebo + MTX	17.2	(3.8; 78.5)	<0.001
ETN 50 mg + MTX / ETN 25 mg + MTX	1.5	(0.4; 6.1)	0.557
ETN 25 mg + MTX / Placebo + MTX	11.3	(3.1; 41.9)	<0.001
Week 18			
ETN 50 mg + MTX / Placebo + MTX	11.0	(2.7; 45.2)	<0.001
ETN 50 mg + MTX / ETN 25 mg + MTX	1.8	(0.5; 6.0)	0.376
ETN 25 mg + MTX / Placebo + MTX	6.3	(1.8; 22.3)	0.004
Week 24			
ETN 50 mg + MTX / Placebo + MTX	9.1	(2.4; 35.1)	0.001
ETN 50 mg + MTX / ETN 25 mg + MTX	1.7	(0.5; 5.4)	0.382
ETN 25 mg + MTX / Placebo + MTX	5.4	(1.5; 19.1)	0.009
Week 30			
ETN 50 mg + MTX / Placebo + MTX	8.6	(2.1; 35.0)	0.003
ETN 50 mg + MTX / ETN 25 mg + MTX	1.3	(0.4; 4.1)	0.609
ETN 25 mg + MTX / Placebo + MTX	6.5	(1.7; 25.2)	0.007
Week 36			
ETN 50 mg + MTX / Placebo + MTX	8.6	(2.1; 35.2)	0.003
ETN 50 mg + MTX / ETN 25 mg + MTX	1.8	(0.6; 5.7)	0.300
ETN 25 mg + MTX / Placebo + MTX	4.7	(1.2; 18.9)	0.028
Week 42			
ETN 50 mg + MTX / Placebo + MTX	8.6	(2.1; 35.3)	0.003
ETN 50 mg + MTX / ETN 25 mg + MTX	1.8	(0.6; 5.5)	0.320
ETN 25 mg + MTX / Placebo + MTX	4.8	(1.2; 19.4)	0.026
Week 48			
ETN 50 mg + MTX / Placebo + MTX	7.2	(1.7; 29.8)	0.007
ETN 50 mg + MTX / ETN 25 mg + MTX	1.7	(0.5; 5.4)	0.362
ETN 25 mg + MTX / Placebo + MTX	4.2	(1.0; 17.0)	0.044

CI = confidence interval; ETN = etanercept; G = Generalized estimating equations model using an auto-regressive correlation structure; mITT = modified intent-to-treat; MTX = methotrexate.

Secondary Endpoint Results:

- Time From Randomization to Failure: The estimated median time from randomization to failure is summarized in Table 7.

Table 7. Time (Weeks) From Randomization to Failure-Kaplan-Meier Analysis-Period 2-mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)
Number of events	11 (48%)	15 (56%)	20 (87%)
Number of censored events	12 (52%)	12 (44%)	3 (13%)
Median time to failure (Weeks) (95% CI)	48.0 (18.1;NE)	36.1 (15.6;NE)	6.1 (4.0;8.4)
Kaplan-Meier survival estimate (SD)*	45% (0.13)	39% (0.11)	12% (0.07)

*Estimate of the percentage of subjects who would not have failed by the end of Period 2, at Week 48.
CI = confidence interval; ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate; N = total number of subjects; SD = standard deviation; NE = not evaluable.

The difference between active treatment groups and placebo group was statistically significant while there was no statistically significant difference between full and reduced dose of ETN. The results are summarized in Table 8.

Table 8. Time (Weeks) From Randomization to Failure-Estimated Hazard Ratios-Period 2-mITT Set

		Hazard Ratio	
Comparison	**Estimate**	**(95% CI)**	**p-Value (C)**
ETN 50 mg + MTX / Placebo + MTX	0.24	(0.10;0.56)	0.001
ETN 50 mg + MTX / ETN 25 mg + MTX	1.01	(0.43;2.35)	0.988
ETN 25 mg + MTX / Placebo + MTX	0.23	(0.11;0.51)	<0.001

C = Cox proportional hazards regression model; CI = confidence interval; ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate.

- Proportion of Subjects in Remission or LDA State at Each Visit: During Period 2, the number of subjects classified as failures and thus entering Period 3 occurred more frequently and more rapidly in the placebo treated group compared to the active treatment groups (Table 9). As a result and due to the sparsity of subjects as the study advanced, particularly in the placebo treatment group, the treatment groups could only be formally compared with a statistical model at Week 6 and Week 12. At Week 6, the odds of being in remission or LDA state in ETN 50 mg + MTX group were significantly greater than in the placebo + MTX group (p=0.043).

Table 9. Proportion of Subjects in Remission or LDA State at Each Visit- Based on Calculated DAS28-Observed Data-Period 2-mITT Set

Time Point		ETN 50 mg + MTX (N=23)			ETN 25 mg + MTX (N=27)			Placebo + MTX (N=23)		
		Remission/LDA (DAS28 ≤3.2)	DAS28 >3.2	Missing	Remission/LDA (DAS28 ≤3.2)	DAS28 >3.2	Missing	Remission/LDA (DAS28 ≤3.2)	DAS28 >3.2	Missing
Screening		23 (100%)	-	-	27 (100%)	-	-	23 (100%)	-	-
Period 1										
	Baseline	19 (100%)	-	4	23 (100%)	-	4	19 (100%)	-	4
	Week 4	23 (100%)	-	-	26 (100%)	-	1	23 (100%)	-	-
Period 2										
	Randomization	22 (100%)	-	1	26 (96%)	1 (4%)	-	23 (100%)	-	-
	Week 6	19 (90%)	2 (10%)	1	21 (81%)	5 (19%)	1	9 (60%)	6 (40%)	-
	Week 12	17 (94%)	1 (6%)	1	18 (86%)	3 (14%)	1	5 (83%)	1 (17%)	-
	Week 18	14 (88%)	2 (13%)	1	17 (89%)	2 (11%)	-	3 (100%)	-	-
	Week 24	14 (100%)	-	1	16 (100%)	-	-	3 (100%)	-	-
	Week 30	13 (93%)	1 (7%)	1	15 (100%)	-	-	2 (67%)	1 (33%)	-
	Week 36	13 (100%)	-	-	12 (86%)	2 (14%)	-	2 (100%)	-	-
	Week 42	12 (100%)	-	1	12 (100%)	-	-	2 (100%)	-	-
	Week 48	10 (83%)	2 (17%)	-	11 (92%)	1 (8%)	-	2 (100%)	-	-
	Endpoint (LOCF)	14 (61%)	9 (39%)	-	15 (56%)	12 (44%)	-	6 (26%)	17 (74%)	-

DAS28 = Disease Activity Score based on a 28-joint count; ETN = etanercept; LDA = Low Disease Activity; LOCF = Last Observation Carried Forward; mITT = modified intent-to-treat; MTX = methotrexate; N = total number of subjects.

- Proportion of Time Subjects were in Remission or LDA State: The results are summarized in Table 10. In the active treatment groups, more than 59% of the subjects were in remission or LDA state at all visits performed during Period 2 compared to 47% of the subjects in the placebo group.

Table 10. Proportion of Time Subjects Were in Remission or LDA State-Observed Data-Period 2-mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)
Proportion of time subjects were in remission or LDA state (%)			
Mean (SD)	83 (31)	75 (38)	55 (49)
Median (Min; Max)	100 (0;100)	100 (0;100)	80 (0;100)
in classes:			
<100%	8 (36%)	11 (41%)	8 (53%)
=100%	14 (64%)	16 (59%)	7 (47%)
Missing data	1	-	8

ETN = etanercept; LDA = Low Disease Activity; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; SD = standard deviation.

- Change from Randomization in DAS28 at Each Visit: The changes from randomization in calculated DAS28 are presented in Table 11. There was a statistically significant difference between the ETN 50 mg + MTX group and the ETN 25 mg + MTX group at Week 24 (p=0.047) and Week 36 (p=0.016) with an adjusted mean difference (95%CI) in change from randomization of DAS28 of -0.7 (-1.3; -0.0) at Week 24 and -0.8 (-1.5; - 0.2) at Week 36.

Table 11. Change in Calculated DAS28 at Each Visit-Period 2-mITT Set

	Adjusted Change From Randomization			Adjusted Difference		
	n	Mean	SE	Pairwise Comparison	Mean (95% CI)	p-value (M)
Week 6						
ETN 50 mg + MTX	21	0.1	0.24	ETN 50 mg + MTX / Placebo + MTX	-0.7 (-1.6;0.1]	0.082
ETN 25 mg + MTX	26	0.5	0.25	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.4 (-0.9;0.2)	0.217
Placebo + MTX	15	0.9	0.36	ETN 25 mg + MTX / Placebo + MTX	-0.4 (-1.2;0.5)	0.363
Week 12						
ETN 50 mg + MTX	17	0.4	0.25	ETN 50 mg + MTX / Placebo + MTX	-1.0 (-2.1;0.2)	0.103
ETN 25 mg + MTX	21	0.3	0.26	ETN 50 mg + MTX / ETN 25 mg + MTX	0.1 (-0.6;0.7)	0.852
Placebo + MTX	6	1.3	0.53	ETN 25 mg + MTX / Placebo + MTX	-1.0 (-2.2;0.2)	0.087
Week 18						
ETN 50 mg + MTX	15	0.4	0.25	ETN 50 mg + MTX / Placebo + MTX	-0.7 (-2.2;0.7)	0.315
ETN 25 mg + MTX	19	0.6	0.27	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.2 (-0.9;0.4)	0.472
Placebo + MTX	3	1.1	0.69	ETN 25 mg + MTX / Placebo + MTX	-0.5 (-2.0;1.0)	0.489
Week 24						
ETN 50 mg + MTX	14	-0.0	0.26	ETN 50 mg + MTX / Placebo + MTX	-1.0 (-2.5;0.4)	0.164
ETN 25 mg + MTX	16	0.7	0.28	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.7 (-1.3;-0.0)	0.047
Placebo + MTX	3	1.0	0.69	ETN 25 mg + MTX / Placebo + MTX	-0.4 (-1.8;1.1)	0.615
Week 30						
ETN 50 mg + MTX	14	0.2	0.26	ETN 50 mg + MTX / Placebo + MTX	-0.9 (-2.4;0.6)	0.227
ETN 25 mg + MTX	15	0.7	0.28	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.5 (-1.2;0.2)	0.132
Placebo + MTX	3	1.1	0.69	ETN 25 mg + MTX / Placebo + MTX	-0.4 (-1.9;1.1)	0.601
Week 36						
ETN 50 mg + MTX	13	0.2	0.26	ETN 50 mg + MTX / Placebo + MTX	-0.3 (-2.0;1.4)	0.741
ETN 25 mg + MTX	14	1.0	0.28	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.8 (-1.5;-0.2)	0.016
Placebo + MTX	2	0.5	0.80	ETN 25 mg + MTX / Placebo + MTX	0.6 (-1.2;2.3)	0.514
Week 42						
ETN 50 mg + MTX	12	0.1	0.27	ETN 50 mg + MTX / Placebo + MTX	-0.9 (-2.6;0.8)	0.296
ETN 25 mg + MTX	12	0.5	0.29	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.3 (-1.0;0.4)	0.370
Placebo + MTX	2	1.0	0.80	ETN 25 mg + MTX / Placebo + MTX	-0.6 (-2.3;1.1)	0.501
Week 48						
ETN 50 mg + MTX	12	0.5	0.27	ETN 50 mg + MTX / Placebo + MTX	-0.7 (-2.4;1.0)	0.394
ETN 25 mg + MTX	12	0.9	0.29	ETN 50 mg + MTX / ETN 25 mg + MTX	-0.5 (-1.1;0.2)	0.186
Placebo + MTX	2	1.2	0.80	ETN 25 mg + MTX / Placebo + MTX	-0.3 (-2.0;1.5)	0.761

CI = confidence index; DAS28 = Disease Activity Score based on a 28-joint count; ETN = etanercept; M = mixed model for repeated measures; mITT = modified intent-to-treat; MTX = methotrexate; n = number of subjects in the specified group; SE = standard error.

- Change From Randomization in Tender and Swollen Joint Counts: At randomization, the median number of tender joints (Table 12) and of swollen joints (Table 13) was 0 in all groups and remained mostly at this level during the whole Period 2, with no statistically significant differences between treatment groups. It must be noted that from Week 18, results of tender and swollen joint counts were available for no more than 3 subjects in the placebo + MTX group.

Table 12. Joint Assessment: Number of Tender Joints - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Randomization				
n	23	27	23	73
Mean (SD)	0.2 (0.5)	0.4 (0.8)	0.5 (0.8)	0.4 (0.7)
Median	0.0	0.0	0.0	0.0
Min; Max	0; 2	0; 2	0; 3	0; 3
Missing data	0	0	0	0
Change From Randomization to Week 6				
n	22	26	15	63
Mean (SD)	0.5 (1.7)	1.4 (2.8)	2.1 (3.1)	1.3 (2.6)
Median	0.0	0.0	1.0	0.0
Min; Max	-2; 6	-2; 9	0; 9	-2; 9
Missing data	0	1	0	1
Change From Randomization to Week 12				
n	18	21	6	45
Mean (SD)	0.6 (1.5)	0.2 (0.9)	4.5 (9.6)	1.0 (3.7)
Median	0.0	0.0	0.5	0.0
Min; Max	0; 6	-2; 2	0; 24	-2; 24
Missing data	1	1	0	2
Change From Randomization to Week 18				
n	16	19	3	38
Mean (SD)	0.3 (0.7)	0.5 (1.7)	0.0 (0.0)	0.4 (1.3)
Median	0.0	0.0	0.0	0.0
Min; Max	-1; 2	-2; 6	0; 0	-2; 6
Missing data	1	0	0	1
Change From Randomization to Week 24				
n	14	16	3	33
Mean (SD)	0.0 (0.0)	0.3 (0.8)	0.3 (0.6)	0.2 (0.6)
Median	0.0	0.0	0.0	0.0
Min; Max	0; 0	-1; 2	0; 1	-1; 2
Missing data	1	0	0	1
Change From Randomization to Week 30				
n	14	15	3	32
Mean (SD)	0.4 (1.9)	0.5 (2.0)	1.0 (2.6)	0.5 (1.9)
Median	0.0	0.0	0.0	0.0
Min; Max	-1; 7	-2; 7	-1; 4	-2; 7
Missing data	1	0	0	1
Change From Randomization to Week 36				
n	13	14	2	29
Mean (SD)	0.1 (0.3)	0.6 (1.6)	-0.5 (0.7)	0.3 (1.1)
Median	0.0	0.0	-0.5	0.0
Min; Max	0; 1	-2; 4	-1; 0	-2; 4
Missing data	0	0	0	0
Change From Randomization to Week 42				
n	12	12	2	26
Mean (SD)	-0.1 (0.7)	-0.3 (0.6)	-0.5 (0.7)	-0.2 (0.6)
Median	0.0	0.0	-0.5	0.0
Min; Max	-2; 1	-2; 0	-1; 0	-2; 1
Missing data	1	0	0	1
Change From Randomization to Week 48				
n	12	12	2	26
Mean (SD)	-0.1 (0.7)	0.1 (0.7)	0.5 (0.7)	0.0 (0.7)
Median	0.0	0.0	0.5	0.0
Min; Max	-2; 1	-1; 2	0; 1	-2; 2
Missing data	0	0	0	0
Change From Randomization to Endpoint (LOCF)				

Table 12. Joint Assessment: Number of Tender Joints - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
N	23	27	23	73
Mean (SD)	1.5 (2.6)	2.4 (3.1)	5.7 (6.6)	3.1 (4.7)
Median	0.0	1.0	4.0	2.0
Min; Max	-2; 7	-1; 9	0; 24	-2; 24
Missing data	0	0	0	0

ETN = etanercept; LOCF = last observation carried forward; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects in specified area; N = total number of subjects; SD = standard deviation.

Table 13. Joint Assessment: Number of Swollen Joints - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Randomization				
n	23	27	23	73
Mean (SD)	0.3 (0.8)	0.4 (0.8)	0.2 (0.4)	0.3 (0.7)
Median	0.0	0.0	0.0	0.0
Min; Max	0; 3	0; 3	0; 1	0; 3
Missing data	0	0	0	0
Change From Randomization to Week 6				
n	22	26	15	63
Mean (SD)	0.1 (1.2)	0.7 (2.2)	1.1 (1.8)	0.6 (1.8)
Median	0.0	0.0	0.0	0.0
Min; Max	-1; 5	-1; 11	0; 6	-1; 11
Missing data	0	1	0	1
Change From Randomization to Week 12				
n	18	21	6	45
Mean (SD)	0.2 (1.0)	0.2 (0.8)	1.5 (2.3)	0.4 (1.2)
Median	0.0	0.0	1.0	0.0
Min; Max	-1; 4	-1; 3	0; 6	-1; 6
Missing data	1	1	0	2
Change From Randomization to Week 18				
n	16	19	3	38
Mean (SD)	0.2 (0.8)	0.4 (2.3)	0.7 (1.2)	0.3 (1.7)
Median	0.0	0.0	0.0	0.0
Min; Max	-1; 2	-3; 8	0; 2	-3; 8
Missing data	1	0	0	1
Change From Randomization to Week 24				
n	14	16	3	33
Mean (SD)	-0.2 (0.9)	0.1 (0.6)	0.3 (0.6)	0.0 (0.8)
Median	0.0	0.0	0.0	0.0
Min; Max	-3; 1	-1; 1	0; 1	-3; 1
Missing data	1	0	0	1
Change From Randomization to Week 30				
n	14	15	3	32
Mean (SD)	0.2 (1.5)	0.1 (1.2)	1.3 (2.3)	0.3 (1.4)
Median	0.0	0.0	0.0	0.0
Min; Max	-2; 5	-3; 3	0; 4	-3; 5
Missing data	1	0	0	1
Change From Randomization to Week 36				
n	13	14	2	29
Mean (SD)	-0.2 (0.7)	0.1 (0.9)	0.0 (0.0)	0.0 (0.8)
Median	0.0	0.0	0.0	0.0
Min; Max	-2; 1	-1; 3	0; 0	-2; 3
Missing data	0	0	0	0
Change From Randomization to Week 42				
n	12	12	2	26
Mean (SD)	0.3 (1.0)	-0.2 (0.6)	0.0 (0.0)	0.0 (0.8)
Median	0.0	0.0	0.0	0.0
Min; Max	-1; 3	-1; 1	0; 0	-1; 3
Missing data	1	0	0	1
Change From Randomization to Week 48				
n	12	12	2	26
Mean (SD)	-0.2 (0.7)	-0.3 (0.6)	0.5 (0.7)	-0.2 (0.7)
Median	0.0	0.0	0.5	0.0
Min; Max	-2; 1	-2; 0	0; 1	-2; 1
Missing data	0	0	0	0
Change From Randomization to Endpoint (LOCF)				

Table 13. Joint Assessment: Number of Swollen Joints - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
n	23	27	23	73
Mean (SD)	0.6 (1.8)	1.2 (2.7)	2.5 (2.1)	1.4 (2.4)
Median	0.0	0.0	2.0	0.0
Min; Max	-2; 5	-2; 11	0; 7	-2; 11
Missing data	0	0	0	0

ETN = etanercept; LOCF = last observation carried forward; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects in specified area; N = total number of subjects; SD = standard deviation.

- Change in Physician Global Assessment, Subject Global Assessment, Subject Global Health VAS, Subject Pain VAS and Morning Stiffness at Each Visit: Results for all these assessments were available for 6 subjects at Week 12 and no more than 3 subjects from Week 18 in the placebo + MTX group. Therefore comparisons between groups must be analyzed and interpreted with caution after these time points.

Physician Global Assessment of Disease Activity: Results of physician global assessment of disease activity are presented in Table 14. There was a statistically significant difference between ETN 50 mg + MTX and placebo + MTX at Week 12 (p=0.015), Week 18 (p=0.022) and Week 24 (p=0.038). The difference in change from randomization was also significant between ETN 25 mg + MTX and placebo + MTX at Week 12 (p=0.024). Still these differences must be considered with caution as there were only 6 subjects at Week 12 and 3 subjects at Weeks 18 and 24 in the placebo + MTX group.

Table 14. Physician Global Assessment of Disease Activity-Observed Data-Period 2-mITT Set

	Change From Randomization				
	n	Median	Min; Max	Pairwise Comparison	p-value (M)
Week 6					
ETN 50 mg + MTX	22	1.5	-8.0; 20.5	ETN 50 mg + MTX / Placebo + MTX	0.323
ETN 25 mg + MTX	26	0.3	-7.0; 58.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.935
Placebo + MTX	14	4.0	-9.0; 50.0	ETN 25 mg + MTX / Placebo + MTX	0.365
Week 12					
ETN 50 mg + MTX	18	1.0	-6.0; 17.0	ETN 50 mg + MTX / Placebo + MTX	0.015
ETN 25 mg + MTX	21	0.5	-7.0; 14.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.755
Placebo + MTX	6	6.8	-4.5; 42.0	ETN 25 mg + MTX / Placebo + MTX	0.024
Week 18					
ETN 50 mg + MTX	16	2.5	-11.0; 18.0	ETN 50 mg + MTX / Placebo + MTX	0.022
ETN 25 mg + MTX	19	4.0	-7.0; 32.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.093
Placebo + MTX	3	10.0	-4.0; 16.0	ETN 25 mg + MTX / Placebo + MTX	0.117
Week 24					
ETN 50 mg + MTX	14	1.0	-9.0; 8.0	ETN 50 mg + MTX / Placebo + MTX	0.038
ETN 25 mg + MTX	15	2.0	-7.0; 23.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.222
Placebo + MTX	3	8.0	-5.0; 14.0	ETN 25 mg + MTX / Placebo + MTX	0.131
Week 30					
ETN 50 mg + MTX	14	1.0	-3.0; 55.0	ETN 50 mg + MTX / Placebo + MTX	0.127
ETN 25 mg + MTX	15	0.0	-7.0; 35.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.830
Placebo + MTX	3	5.0	-5.0; 18.0	ETN 25 mg + MTX / Placebo + MTX	0.159
Week 36					
ETN 50 mg + MTX	13	0.0	-4.0; 9.0	ETN 50 mg + MTX / Placebo + MTX	0.394
ETN 25 mg + MTX	14	0.0	-7.5; 36.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.115
Placebo + MTX	2	-6.5	-16.0; 3.0	ETN 25 mg + MTX / Placebo + MTX	0.876
Week 42					
ETN 50 mg + MTX	12	0.3	-6.0; 26.0	ETN 50 mg + MTX / Placebo + MTX	0.420
ETN 25 mg + MTX	12	-1.0	-9.0; 3.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.890
Placebo + MTX	2	-3.0	-6.0; 0.0	ETN 25 mg + MTX / Placebo + MTX	0.460
Week 48					
ETN 50 mg + MTX	12	0.3	-3.0; 16.0	ETN 50 mg + MTX / Placebo + MTX	0.385
ETN 25 mg + MTX	12	-1.8	-8.5; 4.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.900
Placebo + MTX	2	-1.5	-3.0; 0.0	ETN 25 mg + MTX / Placebo + MTX	0.360

ETN = etanercept; M = Mixed model for repeated measures; mITT = modified intent-to-treat; MTX = methotrexate; n = number of subjects in the specified group.

Subject Global Assessment of Disease Activity: At randomization, the median value on VAS of subject global assessment of disease activity was 8 mm, 12 mm, and 13 mm, in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX group respectively on a 0 to 100 mm VAS. Median change from randomization at each time point was around 0 for both active groups and higher in the placebo + MTX group, but to be noted that this was on a very small number of subjects. There was a statistically significant difference only at Week 12 between ETN 50 mg + MTX and placebo + MTX (p=0.006).

Subject General Health VAS: At randomization, the mean standard deviation value on VAS of subject general health assessment was 14 (13) mm, 15 (13) mm and 19 (15) mm in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX groups respectively. Adjusted mean change of VAS score from randomization at each time point was not significantly different between treatment groups (Table 15).

Table 15. Subject General Health VAS - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Randomization				
n	23	27	23	73
Mean (SD)	14.43 (12.87)	15.11 (13.15)	18.52 (15.35)	15.97 (13.72)
Median	11.00	10.50	16.00	14.00
Min; Max	0.0; 40.0	0.0; 44.0	0.0; 58.5	0.0; 58.5
Missing data	0	0	0	0
Change From Randomization to Week 6				
n	22	26	15	63
Mean (SD)	6.02 (16.67)	6.65 (19.25)	6.40 (19.21)	6.37 (18.08)
Median	4.50	0.00	3.00	2.00
Min; Max	-24.0; 47.0	-22.0; 52.0	-22.5; 45.5	-24.0; 52.0
Missing data	0	1	0	1
Change From Randomization to Week 12				
n	18	21	6	45
Mean (SD)	0.28 (12.49)	3.62 (15.75)	17.58 (28.09)	4.14 (17.13)
Median	0.00	0.00	10.00	0.00
Min; Max	-22.0; 24.0	-24.0; 33.0	-13.5; 54.0	-24.0; 54.0
Missing data	1	1	0	2
Change From Randomization to Week 18				
n	16	19	3	38
Mean (SD)	3.19 (17.49)	2.26 (13.74)	6.83 (19.25)	3.01 (15.41)
Median	0.50	3.00	7.00	1.00
Min; Max	-21.0; 52.0	-26.0; 26.0	-12.5; 26.0	-26.0; 52.0
Missing data	1	0	0	1
Change From Randomization to Week 24				
n	14	16	3	33
Mean (SD)	4.43 (14.37)	0.03 (11.24)	-4.50 (2.78)	1.48 (12.32)
Median	0.50	1.25	-4.00	-1.00
Min; Max	-21.0; 35.0	-20.0; 17.0	-7.5; -2.0	-21.0; 35.0
Missing data	1	0	0	1
Change From Randomization to Week 30				
n	14	15	3	32
Mean (SD)	3.32 (17.06)	3.00 (12.04)	2.50 (27.29)	3.09 (15.35)
Median	0	3	-12.5	1
Min.; Max.	-24.0; 52.0	-25.0; 17.5	-14.0; 34.0	-25.0; 52.0
Missing data	1	0	0	1
Change From Randomization to Week 36				
n	13	14	2	29
Mean (SD)	2.96 (15.04)	5.39 (14.84)	-8.75 (19.45)	3.33 (15.01)
Median	1.00	4.50	-8.75	3.00
Min; Max	-27.0; 32.0	-23.0; 41.0	-22.5; 5.0	-27.0; 41.0
Missing data	0	0	0	0
Change From Randomization to Week 42				
n	12	12	2	26
Mean (SD)	1.42 (17.44)	0.58 (12.37)	20.75 (44.19)	2.52 (17.56)
Median	-0.50	0.50	20.75	0.00
Min; Max	-27.0; 42.0	-22.0; 21.5	-10.5; 52.0	-27.0; 52.0
Missing data	1	0	0	1
Change From Randomization to Week 48				
n	12	12	2	26
Mean (SD)	6.58 (23.73)	3.21 (19.69)	-5.75 (3.89)	4.08 (20.74)
Median	-0.50	0.50	-5.75	-0.50
Min; Max	-24.0; 66.0	-24.0; 53.0	-8.5; -3.0	-24.0; 66.0
Missing data	0	0	0	0
Change From Randomization to Endpoint (LOCF)				

Table 15. Subject General Health VAS - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
n	23	27	23	73
Mean (SD)	14.98 (23.86)	14.28 (21.19)	27.04 (22.70)	18.52 (22.97)
Median	8.00	12.00	24.00	14.00
Min; Max	-24.0; 66.0	-24.0; 53.0	-14.0; 59.5	-24.0; 66.0
Missing data	0	0	0	0

ETN = etanercept; LOCF = last observation carried forward; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects in specified area; N = total number of subjects; SD = standard deviation; VAS = visual analog scale.

VAS Pain: The median pain score assessed by the subject on VAS at randomization was 9 mm, 12 mm and 13 mm in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX groups respectively. Statistically significant differences between treatment groups were observed at a number of time points, summarized in Table 16.

Table 16 VAS Pain-Observed Data-Period 2-mITT Set

	Adjusted Change From Randomization			Adjusted Difference		
	n	Mean	SE	Pairwise Comparison	Mean (95% CI)	p-value (M)
Week 6						
ETN 50 mg + MTX	22	1.9	3.32	ETN 50 mg + MTX / Placebo + MTX	-20.8 [-35.4;-6.2]	0.007
ETN 25 mg + MTX	26	5.7	3.69	ETN 50 mg + MTX / ETN 25 mg + MTX	-3.8 [-12.4;4.8]	0.382
Placebo + MTX	15	22.7	6.39	ETN 25 mg + MTX / Placebo + MTX	-17.0 [-31.9;-2.2]	0.026
Week 12						
ETN 50 mg + MTX	18	-3.1	3.56	ETN 50 mg + MTX / Placebo + MTX	-37.3 [-57.8;-16.9]	<0.001
ETN 25 mg + MTX	21	8.1	3.84	ETN 50 mg + MTX / ETN 25 mg + MTX	-11.1 [-20.3;-1.9]	0.019
Placebo + MTX	6	34.3	9.43	ETN 25 mg + MTX / Placebo + MTX	-26.2 [-46.9;-5.5]	0.015
Week 18						
ETN 50 mg + MTX	16	2.2	3.61	ETN 50 mg + MTX / Placebo + MTX	-10.7 [-36.8;15.4]	0.409
ETN 25 mg + MTX	19	12.2	3.90	ETN 50 mg + MTX / ETN 25 mg + MTX	-10.0 [-19.5;-0.6]	0.038
Placebo + MTX	3	12.9	12.40	ETN 25 mg + MTX / Placebo + MTX	-0.7 [-27.0;25.6]	0.957
Week 24						
ETN 50 mg + MTX	14	-1.2	3.88	ETN 50 mg + MTX / Placebo + MTX	-12.5 [-38.8;13.8]	0.339
ETN 25 mg + MTX	16	7.5	4.06	ETN 50 mg + MTX / ETN 25 mg + MTX	-8.6 [-18.4;1.1]	0.082
Placebo + MTX	3	11.3	12.41	ETN 25 mg + MTX / Placebo + MTX	-3.9 [-30.3;22.6]	0.768
Week 30						
ETN 50 mg + MTX	14	3.2	3.81	ETN 50 mg + MTX / Placebo + MTX	-12.8 [-39.0;13.5]	0.328
ETN 25 mg + MTX	15	7.1	4.08	ETN 50 mg + MTX / ETN 25 mg + MTX	-3.9 [-13.8;5.9]	0.431
Placebo + MTX	3	16.0	12.41	ETN 25 mg + MTX / Placebo + MTX	-8.8 [-35.3;17.6]	0.500
Week 36						
ETN 50 mg + MTX	13	2.1	3.90	ETN 50 mg + MTX / Placebo + MTX	0.6 [-30.0;31.1]	0.969
ETN 25 mg + MTX	14	13.0	4.15	ETN 50 mg + MTX / ETN 25 mg + MTX	-11.0 [-21.0;-0.9]	0.034
Placebo + MTX	2	1.5	14.49	ETN 25 mg + MTX / Placebo + MTX	11.5 [-19.2;42.3]	0.449
Week 42						
ETN 50 mg + MTX	12	1.1	4.02	ETN 50 mg + MTX / Placebo + MTX	-6.1 [-36.7;24.6]	0.688
ETN 25 mg + MTX	12	12.8	4.26	ETN 50 mg + MTX / ETN 25 mg + MTX	-11.8 [-22.1;-1.4]	0.026
Placebo + MTX	2	7.1	14.49	ETN 25 mg + MTX / Placebo + MTX	5.7 [-25.2;36.6]	0.707
Week 48						
ETN 50 mg + MTX	12	1.3	4.06	ETN 50 mg + MTX / Placebo + MTX	-5.2 [-35.9;25.6]	0.733
ETN 25 mg + MTX	12	9.1	4.28	ETN 50 mg + MTX / ETN 25 mg + MTX	-7.8 [-18.2;2.5]	0.137
Placebo + MTX	2	6.5	14.50	ETN 25 mg + MTX / Placebo + MTX	2.7 [-28.2;33.6]	0.861

CI = confidence interval; ETN = etanercept; M = Mixed model for repeated measures; mITT = modified intent-to-treat; MTX = methotrexate; n = number of subjects in the specified group; SE = standard error; VAS = visual analog scale.

Morning Stiffness: At randomization, the median duration of morning stiffness was 10, 1, and 5 minutes in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX groups respectively (Table 17). In both active treatment groups, the median change from randomization was 0 at all-time points. A statistically significant difference in change from randomization was only observed at Week 12 between ETN 50 mg + MTX and placebo + MTX (p=0.009) and between ETN 25 mg + MTX and placebo + MTX (p=0.050) with a median increase of 1 minute in duration of morning stiffness in the placebo group.

Table 17. Morning Stiffness Duration (Minutes) - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Randomization				
n	23	26	23	72
Mean (SD)	29.2 (51.6)	20.3 (48.3)	20.3 (36.8)	23.2 (45.6)
Median	10.0	0.5	5.0	5.0
Min; Max	0; 240	0; 240	0; 120	0; 240
Missing data	0	1	0	1
Change From Randomization to Week 6				
n	22	25	15	62
Mean (SD)	2.2 (20.4)	5.8 (28.6)	119.1 (367.9)	31.9 (184.4)
Median	0.0	0.0	0.0	0.0
Min; Max	-60; 50	-30; 120	-5; 1440	-60; 1440
Missing data	0	2	0	2
Change From Randomization to Week 12				
n	18	20	5	43
Mean (SD)	-1.4 (6.8)	73.5 (315.4)	15.2 (25.8)	35.4 (215.4)
Median	0.0	0.0	1.0	0.0
Min; Max	-15; 10	-30; 1410	0; 60	-30; 1410
Missing data	1	2	1	4
Change From Randomization to Week 18				
n	16	19	3	38
Mean (SD)	89.6 (352.1)	75.6 (323.6)	3.3 (10.4)	75.8 (318.9)
Median	0.0	0.0	0.0	0.0
Min; Max	0; 1410	-30; 1410	-5; 15	-30; 1410
Missing data	1	0	0	1
Change From Randomization to Week 24				
n	14	16	3	33
Mean (SD)	-1.8 (8.2)	3.9 (32.7)	-1.7 (2.9)	1.0 (23.2)
Median	0.0	0.0	0.0	0.0
Min; Max	-30; 5	-60; 90	-5; 0	-60; 90
Missing data	1	0	0	1
Change From Randomization to Week 30				
n	14	15	3	32
Mean (SD)	23.8 (88.4)	-6.3 (35.0)	-6.7 (7.6)	6.8 (63.8)
Median	0.0	0.0	-5.0	0.0
Min; Max	-15; 330	-110; 60	-15; 0	-110; 330
Missing data	1	0	0	1
Change From Randomization to Week 36				
n	13	14	2	29
Mean (SD)	-2.3 (4.8)	0.0 (39.1)	-2.5 (3.5)	-1.2 (26.8)
Median	0.0	0.0	-2.5	0.0
Min; Max	-15; 0	-120; 60	-5; 0	-120; 60
Missing data	0	0	0	0
Change From Randomization to Week 42				
n	12	11	2	25
Mean (SD)	0.3 (3.8)	-6.1 (42.3)	-2.5 (3.5)	-2.7 (27.6)
Median	0.0	0.0	-2.5	0.0
Min; Max	-10; 5	-120; 60	-5; 0	-120; 60
Missing data	1	1	0	2
Change From Randomization to Week 48				
n	12	11	2	25
Mean (SD)	1.3 (6.1)	2.8 (21.1)	-5.0 (7.1)	1.4 (14.5)
Median	0.0	0.0	-5.0	0.0
Min; Max	-10; 15	-30; 60	-10; 0	-30; 60
Missing data	0	1	0	1
Change From Randomization to Endpoint (LOCF)				

Table 17. Morning Stiffness Duration (Minutes) - Observed Data – Period 1 and Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
n	23	26	23	72
Mean (SD)	141.5 (409.6)	67.0 (275.8)	355.4 (580.0)	182.9 (445.1)
Median	0.0	0.0	55.0	5.0
Min.; Max.	-60; 1430	-30; 1410	-10; 1440	-60; 1440
Missing data	0	1	0	1

ETN = etanercept; LOCF = last observation carried forward; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects in specified area; N = total number of subjects; SD = standard deviation; VAS = visual analog scale.

- Changes From Randomization in ESR and CRP: At randomization, the median value of ESR was 10, 8, and 8 mm/hour in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX groups respectively. The change from randomization at each visit and the associated pairwise comparisons between treatments groups are presented in Table 18. At randomization, the median value of plasma CRP was 2.0, 3.0, and 1.6 mg/l, in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX groups respectively. Median change from randomization was 0 at all time points for active treatment groups here were no statistically significant differences between treatment groups (Table 19).

Table 18. ESR (mm/hour) - Observed Data – Period 2 - mITT Set

	Change From Randomization				
	n	Median	Min; Max	Pairwise Comparison	p-value (M)
Week 6					
ETN 50 mg + MTX	21	0.0	-8.0; 10.0	ETN 50 mg + MTX / Placebo + MTX	0.019
ETN 25 mg + MTX	26	0.0	-14.0; 26.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.023
Placebo + MTX	15	2.0	-6.0; 26.0	ETN 25 mg + MTX / Placebo + MTX	0.521
Week 12					
ETN 50 mg + MTX	17	0.0	-7.0; 15.0	ETN 50 mg + MTX / Placebo + MTX	0.251
ETN 25 mg + MTX	21	0.0	-8.0; 11.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.757
Placebo + MTX	6	0.5	-8.0; 7.0	ETN 25 mg + MTX / Placebo + MTX	0.345
Week 18					
ETN 50 mg + MTX	15	1.0	-6.0; 25.0	ETN 50 mg + MTX / Placebo + MTX	0.059
ETN 25 mg + MTX	19	1.0	-7.0; 32.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.399
Placebo + MTX	3	2.0	-6.0; 10.0	ETN 25 mg + MTX / Placebo + MTX	0.182
Week 24					
ETN 50 mg + MTX	14	-1.0	-14.0; 10.0	ETN 50 mg + MTX / Placebo + MTX	0.038
ETN 25 mg + MTX	16	0.0	-5.0; 21.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.127
Placebo + MTX	3	1.0	-6.0; 4.0	ETN 25 mg + MTX / Placebo + MTX	0.304
Week 30					
ETN 50 mg + MTX	14	-1.5	-15.0; 23.0	ETN 50 mg + MTX / Placebo + MTX	0.061
ETN 25 mg + MTX	15	0.0	-4.0; 27.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.086
Placebo + MTX	3	1.0	-4.0; 5.0	ETN 25 mg + MTX / Placebo + MTX	0.473
Week 36					
ETN 50 mg + MTX	13	0.0	-7.0; 4.0	ETN 50 mg + MTX / Placebo + MTX	0.155
ETN 25 mg + MTX	14	1.5	-5.0; 45.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.056
Placebo + MTX	2	-2.5	-6.0; 1.0	ETN 25 mg + MTX / Placebo + MTX	0.851
Week 42					
ETN 50 mg + MTX	12	-1.5	-14.0; 1.0	ETN 50 mg + MTX / Placebo + MTX	0.084
ETN 25 mg + MTX	12	0.0	-7.0; 11.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.136
Placebo + MTX	2	-0.5	-4.0; 3.0	ETN 25 mg + MTX / Placebo + MTX	0.428
Week 48					
ETN 50 mg + MTX	12	2.0	-4.0; 36.0	ETN 50 mg + MTX / Placebo + MTX	0.786
ETN 25 mg + MTX	12	1.0	-3.0; 43.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.756
Placebo + MTX	2	-2.5	-6.0; 1.0	ETN 25 mg + MTX / Placebo + MTX	0.649

ESR = erythrocyte sedimentation rate; ETN = etanercept; Min = minimum; Max = maximum; M = Mixed model for repeated measures; mITT = modified intent-to-treat; MTX = methotrexate; n = number of subjects in the specified group.

Table 19. Plasma C-Reactive Protein (mg/L) - Comparison Between Treatment Groups - Period 2 - mITT Set

	Change From Randomization			
	Median	Min; Max	Difference	p-Value (M)
Week 6				
ETN 50 mg + MTX	0.00	-9.0; 59.0	ETN 50 mg + MTX / Placebo + MTX	0.348
ETN 25 mg + MTX	0.00	-33.2; 31.7	ETN 50 mg + MTX / ETN 25 mg + MTX	0.162
Placebo + MTX	0.33	-3.0; 17.9	ETN 25 mg + MTX / Placebo + MTX	0.889
Week 12				
ETN 50 mg + MTX	0.00	-10.0; 44.0	ETN 50 mg + MTX / Placebo + MTX	0.648
ETN 25 mg + MTX	0.00	-63.4; 12.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.439
Placebo + MTX	0.00	-3.0; 4.1	ETN 25 mg + MTX / Placebo + MTX	0.378
Week 18				
ETN 50 mg + MTX	0.00	-4.0; 12.0	ETN 50 mg + MTX / Placebo + MTX	0.138
ETN 25 mg + MTX	0.00	-4.0; 139.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.752
Placebo + MTX	2.74	1.0; 26.4	ETN 25 mg + MTX / Placebo + MTX	0.181
Week 24				
ETN 50 mg + MTX	0.00	-4.0; 1.1	ETN 50 mg + MTX / Placebo + MTX	0.194
ETN 25 mg + MTX	0.00	-3.1; 2.5	ETN 50 mg + MTX / ETN 25 mg + MTX	0.371
Placebo + MTX	1.00	0.2; 4.3	ETN 25 mg + MTX / Placebo + MTX	0.385
Week 30				
ETN 50 mg + MTX	0.00	-3.0; 5.1	ETN 50 mg + MTX / Placebo + MTX	0.109
ETN 25 mg + MTX	0.00	-3.0; 9.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.625
Placebo + MTX	1.20	1.0; 73.6	ETN 25 mg + MTX / Placebo + MTX	0.176
Week 36				
ETN 50 mg + MTX	0.00	-2.0; 2.9	ETN 50 mg + MTX / Placebo + MTX	0.768
ETN 25 mg + MTX	0.00	-5.0; 29.8	ETN 50 mg + MTX / ETN 25 mg + MTX	0.851
Placebo + MTX	0.94	0.0; 1.9	ETN 25 mg + MTX / Placebo + MTX	0.711
Week 42				
ETN 50 mg + MTX	0.00	-3.0; 1.0	ETN 50 mg + MTX / Placebo + MTX	0.091
ETN 25 mg + MTX	0.00	-3.1; 1.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.673
Placebo + MTX	3.49	3.0; 4.0	ETN 25 mg + MTX / Placebo + MTX	0.138
Week 48				
ETN 50 mg + MTX	0.00	-4.0; 45.0	ETN 50 mg + MTX / Placebo + MTX	0.271
ETN 25 mg + MTX	0.00	-5.0; 6.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.571
Placebo + MTX	-1.42	-3.8; 1.0	ETN 25 mg + MTX / Placebo + MTX	0.406

ETN = etanercept; M = Mixed model for repeated measures; Min = minimum; Max = maximum; mITT = modified intent-to-treat; MTX = methotrexate.

- Change From Randomization in mTSS at Week 48: One subject out of the 3 remaining subjects in the placebo + MTX group had a measure of joint space narrowing score and erosion score at Week 48. Median change between randomization and Week 48 in joint narrowing score and erosion score was 0 in both active treatment groups (Table 20). A similar result was observed for the mTSS calculation which combines the 2 scores. At randomization, the median mTSS was 19.5, 54.2, and 23.0, in ETN 50 mg + MTX, ETN 25 mg + MTX, and placebo + MTX, respectively. There was a median of no change from randomization of mTSS in the different treatment groups at Week 48.

Table 20. Modified TSS - Observed Data - Period 2 - mITT Set

	ETN 50 mg + MTX (N=23)	ETN 25 mg + MTX (N=27)	Placebo + MTX (N=23)	Total (N=73)
Randomization				
n	19	22	17	58
Mean (SD)	37.26 (41.56)	69.27 (68.78)	35.44 (30.24)	48.87 (52.95)
Median	19.50	54.25	23.00	31.50
Min; Max	0.5; 176.0	3.5; 219.0	4.0; 89.5	0.5; 219.0
Missing data	4	5	6	15
Change From Randomization to Week 48				
n	9	9	1	19
Mean (SD)	-0.17 (0.35)	-0.28 (0.75)	-1.00 (.)	-0.26 (0.59)
Median	0.00	0.00	-1.00	0.00
Min; Max	-1.0; 0.0	-2.0; 0.5	-1.0; -1.0	-2.0; 0.5
Missing data	3	3	1	7

ETN = etanercept; mITT = modified intent-to-treat; Min = minimum; Max = maximum; MTX = methotrexate; n = number of subjects in specified area; N = total number of subjects; SD = standard deviation; TSS = total sharp score.

- Change From Randomization in MRI Findings at Week 12: MRIs of the dominant hand and wrist (performed at randomization and Week 12) were scored for signs of synovitis (S-score), bone edema (O-score) and bone erosions (E-score) according to Outcome Measures in RA Clinical Trials. There were no statistically significant differences between active treatment groups in terms of the adjusted mean change from randomization of S-score, O-score and E-score, as summarized in Table 21 and Table 22.

Table 21. MRI Findings: S-Score-Period 2-mITT Set

	Adjusted Change From Randomization			Adjusted Difference		
	n	Mean	SE	Pairwise Comparison	Mean (95% CI)	p-value (A)
Signs of Synovitis: S-score						
ETN 50 mg + MTX	15	-0.2	0.56	ETN 50 mg + MTX / Placebo + MTX	0.1 (-2.7;2.9)	0.923
ETN 25 mg + MTX	14	1.4	0.68	ETN 50 mg + MTX / ETN 25 mg + MTX	-1.5 (-3.5;0.5)	0.122
Placebo + MTX	3	-0.3	1.15	ETN 25 mg + MTX / Placebo + MTX	1.7 (-1.2;4.5)	0.229

A = Analysis of Covariance (ANCOVA); CI = confidence interval; ETN = etanercept; mITT = modified intent-to-treat; MRI = Magnetic Resonance Imaging; MTX = methotrexate; n = number of subjects in the specified group; SE = standard error.

Table 22. MRI Findings: O-Score, and E-Score-Period 2-mITT Set

	Change From Randomization to Week 12				
	n	Median	Min; Max	Pairwise Comparison	p-value (A)
Bone Oedema: O-score					
ETN 50 mg + MTX	15	0.0	-2.0; 0.0	ETN 50 mg + MTX / Placebo + MTX	0.898
ETN 25 mg + MTX	14	0.0	-0.5; 2.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.094
Placebo + MTX	3	-3.0	-4.0; 0.5	ETN 25 mg + MTX / Placebo + MTX	0.230
Erosion Score: E-score					
ETN 50 mg + MTX	15	0.0	-1.0; 0.5	ETN 50 mg + MTX / Placebo + MTX	0.538
ETN 25 mg + MTX	14	0.0	-0.5; 4.0	ETN 50 mg + MTX / ETN 25 mg + MTX	0.353
Placebo + MTX	3	0.0	0.0; 0.0	ETN 25 mg + MTX / Placebo + MTX	0.977

A = Analysis of Covariance (ANCOVA); ETN = etanercept; mITT = modified intent-to-treat; MRI = Magnetic Resonance Imaging; MTX = methotrexate; n = number of subjects in the specified group; SE = standard error.

- Potential Predictors of Treatment Failure: The proportion of subjects in treatment failure over 48 weeks was summarized according to potential predictive variables at randomization. According to the multivariate analysis, the risk for failure was higher in subjects randomized in the placebo + MTX group, with a higher erosion score and higher VAS pain score at randomization (Table 23).

Table 23. Influence of Predictor Variables on Treatment Failure-Multivariate Analyses-Final Model-mITT Set

Explanatory Variable-Interpretation	Odds-Ratio (95% CI)	p-value
Treatment assigned by randomization		0.020
ETN 50 mg + MTX (reference)	1.00	
ETN 25 mg + MTX	0.62 (0.13;2.95)	
Placebo + MTX	7.75 (1.34;44.70)	
Erosion score at randomization		
By 1-unit increment	1.05 (1.02;1.09)	0.005
Subject pain VAS at randomization		
By 1-unit increment	1.08 (1.01;1.15)	0.018

CI = confidence interval; ETN = etanercept; mITT = modified intent-to-treat; MTX = methotrexate; VAS = Visual Analog Scale.

Safety Results: AEs occurring during the study are summarized in Table 24.

Table 24. Summary of Safety-All Periods-Safety Set

	Period 1		Period 2						Period 3	
	ETN 50 mg +MTX (N=91)		ETN 50 mg +MTX (N=23)		ETN 25 mg +MTX (N=27)		Placebo + MTX (N=23)		ETN 50 mg +MTX (N=43)	
	No. of Events	n (%) Subjects	No. of Events	n (%) Subjects	No. of events	n (%) Subjects	No. of Events	n (%) Subjects	No. of Events	n (%) Subjects
All AEs	35	27 (30%)	59	16 (70%)	74	20 (74%)	19	7 (30%)	87	31 (72%)
AEs related to study treatment	4	4 (4%)	9	7 (30%)	26	11 (41%)	5	4 (17%)	26	15 (35%)
AEs leading to study withdrawal	-	-	-	-	1	1 (4%)	-	-	-	-
Severe AEs	-	-	-	-	2	2 (7%)	-	-	-	-
SAEs	-	-	1	1 (4%)	1	1 (4%)	-	-	1	1 (2%)
SAEs related to study treatment	-	-	-	-	1	1 (4%)	-	-	1	1 (2%)

AE = adverse event; ETN = etanercept; MTX = methotrexate; N = total number of subjects; n = number of subjects in the specified group; SAE = serious adverse events.

Period 1: A total of 27 subjects (30%) experienced 35 AEs, none of which severe and none considered serious. No AE led to study treatment discontinuation or to study withdrawal. Results are summarized in Table 25. All AEs were considered to be of mild (57%) or moderate (43%) intensity. Most AEs (83%) were resolved at the end of the study, while 6 AEs (17%) were still ongoing. No AE led to hospitalization.

Table 25. Most Frequent Adverse Events-Period 1– Safety Subset Period 1

SOC/Preferred Term	Total (N=91)	
	No. of Events	n (%) subjects
All	35	27 (29.7%)
Infections and infestations	16	13 (14.3%)
Nasopharyngitis	7	7 (7.7%)
Upper respiratory tract infection	3	2 (2.2%)

AEs/SAEs are not separated out.
AEs = adverse events; N = total number of subjects; n = number of subjects in the specified group; SOC = System Organ Class; SAEs = serious adverse events.

Period 2: Forty three of the 73 randomized subjects (59%) experienced at least 1 AE, with a total of 152 AEs experienced by these subjects. The most frequent AEs (reported for more than 1 subject overall) are summarized in Table 26. The majority of AEs experienced in Period 2 were of mild intensity (71%) and 28% were of moderate intensity. Two AEs (1%) were considered severe in intensity; both were experienced by subjects in the ETN 25 mg + MTX group: endometritis and oropharyngeal pain. Both AEs were resolved at the end of the study. Endometritis was considered as a SAE related to study treatment and led to study withdrawal.

Table 26. Most frequent Adverse Events -Period 2-Safety Subset Period 2

Preferred Term	ETN 50 mg +MTX (N=23)		ETN 25 mg +MTX (N=27)		Placebo + MTX (N=23)	
	No. of Events	n (%) Subjects	No. of Events	n (%) Subjects	No. of Events	n (%) Subjects
Nasopharyngitis	8	6 (26%)	14	8 (30%)	2	2 (9%)
Upper respiratory tract infection	7	6 (26%)	9	3 (11%)	2	2 (9%)
Arthralgia	2	2 (9%)	3	3 (11%)	0	0
Headache	3	3 (13%)	1	1 (4%)	1	1 (4%)
Back pain	4[a]	3 (13%)	1	1 (4%)	-	-
Gastroenteritis	-	-	3	3 (11%)	-	-
Pyrexia	-	-	4	3 (11%)	-	-
Bronchitis	1	1 (4%)	1	1 (4%)	-	-
Constipation	1	1 (4%)	1	1 (4%)	-	-
Fatigue	1	1 (4%)	1	1 (4%)	-	-
Haemorrhoids	-	-	2	2 (7%)	-	-
Hypertension	-	-	2	2 (7%)	-	-
Influenza	1	1 (4%)	-	-	1	1 (4%)
Ligament sprain	1	1 (4%)	-	-	1	1 (4%)
Myalgia	2	1 (4%)	2	1 (4%)	-	-
Oropharyngeal pain	-	-	3	2 (7%)	-	-
Osteoporosis	1	1 (4%)	-	-	1	1 (4%)
Pain in extremity	1	1 (4%)	1	1 (4%)	-	-
Rash	-	-	1	1 (4%)	1	1 (4%)
Rhinitis	1	1 (4%)	1	1 (4%)	-	-
Urinary tract infection	-	-	1	1 (4%)	1	1 (4%)

AEs/SAEs are not separated out.
AE = adverse event; ETN = etanercept; MTX = methotrexate; N = total number of subjects; n = number of subjects in the specified group; SAE = serious adverse event.
a. Including 1 SAE.

Period 3: A total of 31 subjects (72%) subjects experienced 87 AEs. All AEs experienced during Period 3 were considered of mild (66%) or moderate (35%) intensity. The majority of the AEs (90%) were resolved at the end of the study (Table 27). Twenty six of these AEs were considered related to study treatment for 15 subjects (35%). One subject experienced an SAE related to study treatment. No AEs led to treatment discontinuation or to study withdrawal.

Table 27. Most Frequent Adverse Events-Period 3-Safety Set Period 3

SOC/Preferred Term	Total (N=43)	
	No. of Events	n (%) Subjects
All	87	31 (72.1%)
Infections and infestations	43	25 (58.1%)
Upper respiratory tract infection	12	9 (20.9%)
Nasopharyngitis	9	8 (18.6%)
Gastroenteritis	3	3 (7.0%)
Respiratory tract infection	3	3 (7.0%)

AEs/SAEs are not separated out.
AE = adverse event; N = total number of subjects; n = number of subjects in the specified group; SOC = System Organ Class; SAE = serious adverse event.

Four subjects (4%) experienced 1 AE related to the study treatment during Period 1: nasopharyngitis for 3 subjects (3%) and pneumonia for 1 subject (Table 28).

Table 28. Treatment Related Adverse Events -Period 1– Safety Subset Period 1

SOC/Preferred Term	Total (N=91)	
	No. of Events	n (%) Subjects
All	4	4 (4%)
Infections and infestations	4	4 (4%)
Nasopharyngitis	3	3 (3%)
Pneumonia	1	1 (1%)

n = number of subjects in the specified group; N = total number of subjects; PT = preferred term; SOC = System Organ Class.

Treatment Related AEs during Period 2 and 3 are summarized in Table 29.

Table 29. Treatment Related Adverse Events – Period 2 and 3

SOC/Preferred Term	Period 2						Period 3	
	ETN 50 mg +MTX (N=23)		ETN 25 mg +MTX (N=27)		Placebo + MTX (N=23)		ETN 50 mg +MTX (N=43)	
	No. of Events	n (%) Subjects	No. of events	n (%) Subjects	No. of Events	n (%) Subjects	No. of Events	n (%) Subjects
All	9	7 (30%)	26	11 (41%)	5	4 (17%)	26	15 (35%)
Infections and infestations	6	4 (17%)	17	8 (30%)	4	3 (13%)	19	13 (30.2%)
Nasopharyngitis	3	3 (13%)	7	5 (19%)	-	-	4	3 (7%)
Upper respiratory tract infection	2	2 (9%)	7	2 (7%)	1	1 (4%)	6	5 (12%)
Acute sinusitis	-	-	-	-	1	1 (4%)	-	-
Bronchitis	-	-	1	1 (4%)	-	-	-	-
Endometritis	-	-	1	1 (4%)	-	-	-	-
Herpes zoster	-	-	1	1 (4%)	-	-	-	-
Oral fungal infection	-	-	-	-	1	1 (4%)	-	-
Oral herpes	1	1 (4%)	-	-	-		-	-
Urinary tract infection	-	-	-	-	1	1 (4%)	-	-
Borrelia infection	-	-	-	-	-	-	1	1 (2%)
Bronchitis	-	-	-	-	-	-	1	1 (2%)
Laryngitis	-	-	-	-	-	-	1	1 (2%)
Pharyngitis	-	-	-	-	-	-	1	1 (2%)
Viral upper respiratory tract infection	-	-	-	-	-	-	1	1 (2%)
Respiratory tract infection	-	-	-	-	-	-	2	2 (5%)
Skin infection	-	-	-	-	-	-	2	2 (5%)
General disorders and administration site conditions	2	2 (9%)	3	3 (11%)	-	-	1	1 (2%)
Pyrexia	-	-	3	3 (11%)	-	-	1	1 (2%)
Influenza like illness	1	1 (4%)	-	-	-	-		
Injection site reaction	1	1 (4%)	-	-	-	-		
Respiratory, thoracic and mediastinal disorders	-	-	3	3 (11%)	-	-	-	-
Oropharyngeal pain	-	-	2	2 (7%)	-	-	-	-
Cough	-	-	1	1 (4%)	-	-	-	-
Musculoskeletal and connective tissue disorders	-	-	2	2 (7%)	-	-		
Bursitis	-	-	1	1 (4%)	-	-		
Exostosis	-	-	1	1 (4%)	-	-		
Gastrointestinal disorders	-	-	1	1 (4%)	-	-	3	1 (2%)
Sigmoiditis	-	-	1	1 (4%)	-	-	3	1 (2%)
Investigations	1	1 (4%)	-	-	-	-	1	1 (2%)
ALT increased	1	1 (4%)	-	-	-	-		
Neutrophil count decreased							1	1 (2%)
Psychiatric disorders	-	-	-	-	1	1 (4%)		
Depression	-	-	-	-	1	1 (4%)		

AEs/SAEs are not separated out.
AE = adverse events; N = total number of subjects; n = number of subjects in specified group; SOC = System Organ Class; SAE = serious adverse events.

Three SAEs were reported in this study: 2 SAEs occurred during Period 2 and 1 SAE occurred during Period 3 (Table 30).

Table 30. Description of Serious Adverse Events-Safety Set

S. No.	Period	Treatment Received	MedDRA Preferred Term	Duration (Days)	Severity	Relationship to the Treatment	Action Taken	Outcome
1.	2	ETN 50 mg + MTX	Back pain	50	Moderate	No	Concomitant medication; Hospitalization	Resolved
2.	2	ETN 25 mg + MTX	Endometritis	17	Severe	Yes	Withdrawn from the study; Concomitant medication; Hospitalization	Resolved
3.	3	ETN 50 mg + MTX	Pyrexia	18	Moderate	Yes	Temporary discontinuation of study treatment; Hospitalization	Resolved

MedDRA = Medical Dictionary for Regulatory Activities; ETN = etanercept; MTX = methotrexate.

There were no AEs leading to study withdrawal or permanent treatment discontinuation reported during Periods 1 and 3.

During Period 2, 1 subject (1%) treated with ETN 25 mg + MTX experienced 1 episode of serious endometritis which led to withdrawal from the study.

No death was reported during the study.

Conclusion: The proportion of non-failures at Week 48 (primary endpoint) was statistically significantly higher in the ETN + MTX groups when compared to placebo + MTX, thus supporting the hypothesis described in the protocol. No differences were detected between the full (ETN 50 mg QW) and reduced dose (ETN 25 mg QW) of ETN. In terms of the secondary efficacy endpoints, both active treatment groups were superior to placebo for estimated time to failure and changes in VAS pain score. Due to the small number of subjects in the placebo + MTX group remaining non-failure over time, comparison between ETN + MTX groups and placebo + MTX group were difficult to analyze after Week 12. Failures returned to remission/LDA when re-treated with ETN 50 mg QW + MTX after a median time of 4 to 6 weeks. According to the multivariate analysis, the risk for failure was higher in subjects randomized in the placebo + MTX group, with a higher erosion score and higher VAS pain score at randomization. Overall, the safety data were as expected.