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

**PROTOCOL NO.:** 0881A-101548 (B1801325)

**PROTOCOL TITLE:** A 24-Month, Randomized, Double-Blind, Two-Period Study To Evaluate The Efficacy And Safety Of The Combination Of Etanercept And Methotrexate And Methotrexate Alone In Subjects With Active Early Rheumatoid Arthritis: Combination Of Methotrexate And Etanercept In Active Early Rheumatoid Arthritis (Comet)

**Study Centers:** A total of 69 centers in 22 countries took part in the study and randomized subjects: Austrailia (4); Belgium (3); Brazil (2); Denmark (2); Finland (2); France (11); Germany (9); Greece (2); Hungary (1); Ireland (2); Italy (8); Mexico (2); The Netherland (4); Norway (2); Portugal (1); Spain (3); Sweden (2); Switzerland (1); Taiwan (2); Turkey (1); The United Kingdom (6) and The United States (1).

**Study Initiation and Final Completion Date:** 01 November 2004 to 11 March 2008

**Phase of Development:** Phase 4

**Study Objectives:**

Primary Objective

To compare the effects of the combination of Etanercept (ETN) and Methotrexate (MTX) to MTX alone on radiographic change and clinical disease activity in subjects with active early Rheumatoid Arthritis (RA) over 12 months.

Secondary Objectives

1. To evaluate the safety of each treatment group over 24 months

2. To compare the effects of the combination of ETN and MTX to MTX alone on radiographic change and clinical disease activity over 12 months in Period 2 in subjects who first received 12 months of MTX alone

3. To compare the effects of the combination of ETN and MTX to ETN alone on radiographic change and clinical disease activity over 12 months in Period 2 in subjects who first received 12 months of the combination of ETN and MTX

4. To compare the effects of the combination of ETN and MTX for 24 months to MTX alone for 12 months followed by the combination of ETN and MTX on radiographic change and clinical disease activity over 24 months

5. To compare the effects of the combination of ETN and MTX to MTX alone on radiographic change and clinical disease activity over 24 months

6. The purpose of the retrospective chart review follow-up is to gain further information about how RA patients are treated in the real world setting.

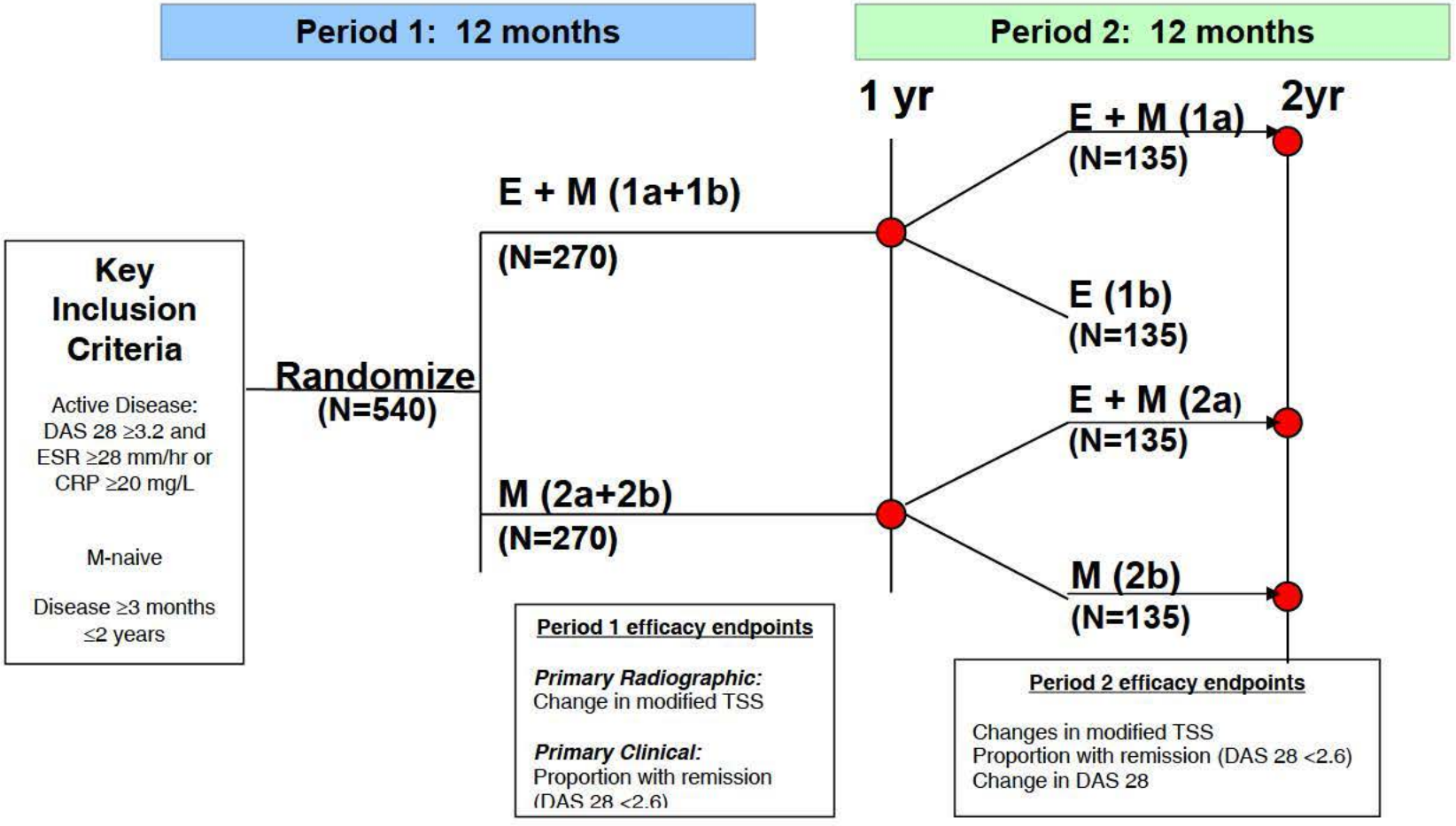
## METHODS

**Study Design:** This was a 24-month, double-blind, randomized, 2-period, parallel-group, multicenter, outpatient study. Period 1 and Period 2 were both 12 months in duration. Approximately 540 subjects were randomized equally to 1 of 4 treatment groups: Group 1a received the combination of ETN and MTX in Period 1 and Period 2. Group 1b received the combination of ETN and MTX in Period 1 and ETN alone in Period 2. Group 2a received MTX alone in Period 1 and the combination of ETN and MTX in Period 2. Group 2b received MTX alone in Period 1 and Period 2. Investigators and subjects remained blinded to treatment assignments until Period 2 was completed and the data from that period was analyzed.

For Period 1 of this study combination of MTX and ETN in active early rheumatoid arthritis (COMET) was designed to directly compare the effectiveness of combination therapy with MTX+ETN and single-agent therapy with MTX in subjects with active early RA (duration of disease of ≤2 years). During the second year of the study (Period 2), subjects were evaluated to determine whether treatment with combination therapy improved radiographic and clinical disease activity of RA among subjects treated initially with MTX alone, whether ETN alone was effective in maintaining the same RA disease activity as the combination therapy, and whether additional benefit was achieved by adding ETN to MTX monotherapy.

Efficacy and safety assessments were made at frequent and regular intervals throughout the study. Radiographs of hands, wrists, and forefeet were taken at Baseline, Week 52, and Week 104 or the final study visit. Digitized images of the radiographic films for each subject were read by 2 independent physicians in a randomized sequence and scored for erosions and joint space narrowing (JSN). The readers were blinded to treatment group throughout the entire reading process. The study design is represented schematically in Figure 1. Evaluations during the first period of the study were performed according to the flowchart of study assessments presented in Table 1. The approximate duration of subject participation was 25 months and the total duration of this study was approximately 40 months.

**Figure 1. COMET Study Schema**



CRP = C-reactive protein; COMET = combination of methotrexate and etanercept in active early rheumatoid arthritis; DAS 28 = disease activity score in 28 joints; E= etanercept; ESR = erythrocyte sedimentation rate; M = methotrexate; TSS = total Sharp Score.

## Table 1. Study Flowchart, Period 1

| Visit Description | Screening | Baseline | Routine Study Visits | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** |
| **Week in Period 1[a]** | **-4[b]** | **0** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **36** | **44** | **52 (Month 12)[c]** |
| Sign informed consent form | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | |
| Physical examination | X | | | | | X | | | X | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body weight and height | X | | | | | | | | | | | | X |
| Evaluation of adverse events[d] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Record prior medications | X | | | | | | | | | | | | |
| Record prior DMARDs / Corticosteroids | X | | | | | | | | | | | | |
| Record concomitant medications | | X | X | X | X | X | X | X | X | X | X | X | X |
| Chest radiograph | X | | | | | | | | | | | | |
| Joint assessment (complete joint count by the investigator) | X | X | X | X | X | X | X | X | X | | X | | X |
| Morning stiffness | X | X | X | X | X | X | X | X | X | | X | | X |
| Physician global assessment | | X | X | X | X | X | X | X | X | | X | | X |
| Patient global assessment | | X | X | X | X | X | X | X | X | | X | | X |
| Patient general health VAS | X | X | X | X | X | X | X | X | X | | X | | X |
| Patient pain VAS | | X | X | X | X | X | X | X | X | | X | | X |
| Patient fatigue VAS | | X | X | X | X | X | X | X | X | | X | | X |
| HAQ | | X | | | | X | | | X | | X | | X |
| SF-36 questionnaire | | X | | | | X | | | X | | X | | X |
| EQ-5D health questionnaire | | X | | | | X | | | X | | X | | X |
| HADS assessment | | X | | | | X | | | X | | X | | X |
| Employment status questions | | X | | | | X | | | X | | X | | X |
| CRP | X | X | X | X | X | X | X | X | X | | X | | X |
| ESR | X | X | X | X | X | X | X | X | X | | X | | X |
| RF | | X | | | | | | | | | | | X |
| CCP antibody | | X | | | | | | | | | | | X |
| Chemistry/hematology/urinalysis | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Table 1. Study Flowchart, Period 1

| Visit Description | Screening | Baseline | Routine Study Visits | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** |
| **Week in Period 1[a]** | **-4[b]** | **0** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **36** | **44** | **52 (Month 12)[c]** |
| Pregnancy test[e] | X | X | | | | | | | | | | | |
| Hand, wrist, and forefoot radiographs | | X | | | | | | | | | | | X |
| Dispense test article | | X | | X | X | X | X | X | X | X | X | X | X |

CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = Euro-Qol; ESR = erythrocyte sedimentation rate; HADS = hospital anxiety depression scale; HAQ = health assessment questionnaire; RF = rheumatoid factor; VAS = visual analog scale.

a. The visit window for Visits 2 through 12 was ±4 days. Visit 13 (Week 52) was to occur 12 months ±2 weeks after the Baseline Visit (Week 0).
b. Not more than 4 weeks before the Baseline visit.
c. For subjects who prematurely withdrew from the study, final visit procedures were to be performed at the time of premature withdrawal. For subjects who withdrew prior to Month 12, the investigator was to attempt to obtain radiographs at the 12-month and 24-month time points (with a ±1-month window). For subjects who withdrew prior to Month 24 but after Month 12, the investigator was to attempt to obtain radiographs at the 24-month time point (with a ±1-month window). If radiographs for the study had been obtained within 1 month of the 12-month or 24-month time points, they did not have to be repeated. Subjects who had surgery involving joints of the hands or feet during the course of the study were exempt from the requirement to obtain 12-month and 24-month radiographs.
d. Adverse events were to be reported from the time of signing the informed consent form.
e. For women of childbearing potential only (serum test at the Screening Visit, urine test at the Baseline Visit). Pregnancy testing (serum or urine test) was repeated after the Baseline Visit at the discretion of the investigator.

Evaluations during the second year of the study were performed according to the flowchart of study assessments presented in Table 2.

**Table 2. Study Flowchart, Period 2**

| Visit Description | Routine Study Visits | | | | | | Final |
|---|---|---|---|---|---|---|---|
| **Visit Number** | **14** | **15** | **16** | **17** | **18** | **19** | **20[a]** |
| **Months in Period 2 (Cont'd from Period 1)[b]** | **13** | **14** | **16** | **18** | **20** | **22** | **24[a],[c]** |
| Physical examination | | | X | | X | | X |
| Vital signs | | X | X | X | X | X | X |
| Body weight and height | | | | | | | X |
| Evaluation of adverse events | X | X | X | X | X | X | X |
| Record concomitant medications | | X | X | X | X | X | X |
| Joint assessment (complete joint count by the investigator) | | | X | | X | | X |
| Morning stiffness | | | X | | X | | X |
| Physician global assessment | | | X | | X | | X |
| Patient global assessment | | | X | | X | | X |
| Patient general health VAS | | | X | | X | | X |
| Patient pain VAS | | | X | | X | | X |
| Patient fatigue VAS | | | X | | X | | X |
| HAQ | | | X | | X | | X |
| SF-36 questionnaire | | | X | | X | | X |
| EQ-5D health questionnaire | | | X | | X | | X |
| HADS assessment | | | X | | X | | X |
| Employment status questions | | | X | | X | | X |
| CRP | | | X | | X | | X |
| ESR | | | X | | X | | X |
| RF | | | | | | | X |
| CCP antibody | | | | | | | X |
| Chemistry/hematology/urinalysis | | X | X | X | X | X | X |
| Hand, wrist, and forefoot radiographs | | | | | | | X |
| Dispense test article | X | X | X | X | X | X | |

AE = adverse event; CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; EQ-5D = Euro-Qol; ESR = erythrocyte sedimentation rate; HADS = hospital anxiety depression scale; HAQ = health assessment questionnaire; RF = rheumatoid factor; SAE = serious adverse event; VAS = visual analog scale.

a. For subjects who prematurely withdrew from the study, final visit procedures were to be performed at the time of premature withdrawal. For subjects who withdrew prior to Month 12, the investigator was to attempt to obtain radiographs at the 12-Month and 24-Month time points (with a ±1-month window). For subjects who withdrew prior to Month 24 but after Month 12, the investigator was to attempt to obtain radiographs at the 24-Month time point (with a ±1-month window). If radiographs for the study had been obtained within 1 Month of the 12-month or 24-month time points, they did not have to be repeated for that time point. Subjects who had surgery involving joints of the hands or feet (during the course of the study) were exempted from the requirement to obtain 12-Month and 24-Month radiographs.

b. The visit window for Visits 14 through 19 was ±1 week. Visit 20 (month 24) was to occur 12 Months ±2 weeks after Visit 13 (Month 12).

c. A follow-up phone call was to be performed approximately 15 days after the final/early-withdrawal visit to assess the occurrence of AEs and SAEs since the previous study visit.

**Number of Subjects (Planned and Analyzed):** Approximately 540 subjects were planned for randomization equally to 1 of 4 treatment groups, 2 groups for each study period. A total of 542 subjects were enrolled in Year 1 of these, 268 subjects were randomized to the MTX treatment group and 274 subjects were randomized to the ETN + MTX treatment group. All 542 enrolled subjects received at least 1 dose of test article.

A total of 411 subjects were enrolled in the Year 2 of this study. One hundred eleven (111) subjects were randomly assigned to the ETN+MTX/ETN+MTX treatment group, 90 to the MTX/MTX+ETN treatment group, 111 to the ETN+MTX/ETN treatment group, and 99 to the MTX/MTX treatment group. All 411 enrolled subjects received at least 1 dose of test article by Year 2.

**Diagnosis and Main Criteria for Inclusion:** Eligible subjects were male and female with of 18 years and older and satisfied the 1987 American College of Rheumatology (ACR) revised criteria for RA and had RA ≥3 months and ≤2 years.

Subjects were excluded from study if they received any previous treatment with MTX and if they received any previous treatment with ETN or other tumor necrosis factor antagonist.

**Study Treatment:** ETN was supplied in vials as a sterile lyophilized powder containing 25 mg of ETN. Methotrexate was supplied as opaque, grey capsules containing MTX sodium equivalent to 2.5 mg of MTX per capsule. All subjects received ETN 50 mg subcutaneous (SC) injections or ETN-matching placebo SC injections once weekly, and MTX orally, or MTX-matching placebo once weekly. The dose of ETN was given as 2 separate injections of 25 mg each, given on the same day at different sites, once weekly.The following 4 treatment groups were included in Period 2 of the study: (ETN+MTX/ETN+MTX), (MTX/ETN+MTX), (ETN+MTX/ETN), and (MTX/MTX).

**Efficacy Endpoints:**

Primary Endpoints:

Primary Radiographic Efficacy Endpoint:

Change in modified Total Sharp Score (TSS) over 12 months (modified TSS: joint erosion score plus JSN score).

Primary Clinical Efficacy Endpoint

Proportion of patients achieving disease activity score in 28 joints (DAS28) remission (defined as a DAS28 score <2.6) at Month 12.

Secondary Endpoints:

Secondary Radiographic Endpoints:

- Change in modified TSS from Month 12 to Month 24 (Period 2)
- Change in modified TSS from Baseline to Month 24
- Proportion of subjects achieving DAS28 remission at Month 24

Secondary Clinical Efficacy Endpoint:

- Change in DAS28 value from Month 12 to Month 24 (Period 2)
- Change in DAS28 value from Baseline to Month 24

**Safety Evaluations**: Safety results of this study, including AEs, clinical laboratory evaluations, other laboratory evaluations, and vital signs and body weight measurements.

**Statistical Methods:**

Intent-To-Treat Population

The Intent-To-Treat (ITT) population was defined as all enrolled subjects in the trial who received at least 1 dose of test article. For subjects who were included in the radiographic ITT population but did not complete Year 2, Year 2 values were imputed by linear extrapolation from the time of the final on-therapy evaluation. For the analysis, Year 2 values were adjusted by linear extrapolation to represent the 2-year change (ie, 365 × 2 × [observed change/days between readings]). Year 1 values did not need to be extrapolated since all subjects in the radiographic ITT population completed Year 1.

Modified Intent-To-Treat Population

The Modified Intent-To-Treat Efficacy (mITT) population included all enrolled subjects who received at least 1 dose of test article and reported both Baseline and on-therapy efficacy results. This population was the population of primary interest for efficacy. Similarly, the mITT population for Year 2 (only) analyses included all enrolled subjects who received at least 1 dose of test article, reported both the Year 2 Baseline and at least 1 postyear 1-Baseline on-therapy DAS 28 results. For other endpoints, fewer subjects wereincluded if they were missing data for that particular endpoint. There were 2 baselines for year 2 analyses: 1 was the original Baseline of the study; the other was the observations on visit 13 (week 52). Therefore, mITT population for the 1 to 104 week analyses included all enrolled subjects who received at least 1 dose of test article, reported both year 1 Baseline and at least 1 postyear 1-Baseline on-therapy results. Separate mITT populations were defined for clinical efficacy and radiographic efficacy analyses. For the clinical efficacy analysis the presence of Baseline and on-therapy DAS 28 was used to define the mITT population, and for the radiographic mITT population valid Baseline and postbaseline TSS were required. One (1) site, site 526, was closed prematurely because of Good clinical practice compliance

violations and subjects from this site were excluded from the efficacy and patient-reported outcomes analyses.

Valid-For-Efficacy Population

The Valid-For-Efficacy (VFE) population was defined as the subset of the mITT population who had no protocol violations that would affect the assessment of efficacy. A decision to define a VFE population was made before the database was locked.

A subject was defined as evaluable, (ie, included in the radiographic ITT population) if he/she received at least 1 dose of one of the assigned test articles and provided data for Baseline, Week 52 and Week 104, or for the early termination visit.

Unless otherwise stated, all statistical tests were 2-sided tests performed at the 0.05 significance level.

Analysis of Efficacy Endpoints

The primary radiographic efficacy endpoint was the change in modified TSS from Baseline to Month 12. The primary clinical efficacy endpoint was the proportion of subjects achieving remission (ie, DAS 28 value of <2.6 at 12 months). The radiographic efficacy endpoint and the clinical efficacy endpoint were analyzed as coprimary endpoints, and the Hochberg step-up procedure was used to adjust for multiple comparisons.

Continuous endpoints were analyzed as change from Baseline using analysis of covariance (ANCOVA), with Baseline value as covariate when Baseline value was known, or using analysis of variance (ANOVA) on observed scores when there was no Baseline value. The ANCOVA models also included factors for study region and treatment. Endpoints that measured the proportions of subjects were compared using the Fisher exact test. For each treatment group, the change from Baseline efficacy endpoints were analyzed to determine if their mean estimate was significantly different from 0 using the nonparametric Wilcoxon signed-rank test.

The following statistical comparisons were applied to the data:

1. ETN+MTX/ETN+MTX (Group 1a) and ETN+MTX/ETN (Group 1b) over 12 months in Period 2, ie, from Month 12 to Month 24, with the alternative hypotheses that there was difference.

2. MTX/ETN+MTX (Group 2a) and MTX/MTX (Group 2b) alone over 12 months in Period 2, ie, from Month 12 to Month 24, with the alternative hypotheses that there was difference.

3. ETN+MTX/ETN+MTX (group 1a) and MTX/ETN+MTX (Group 2a) over 24 months, ie, from Baseline to Month 24, with the alternative hypotheses that there was difference.

4. ETN+MTX/ETN+MTX (Group 1a) and MTX/MTX (Group 2b) over 24 months, ie, from Baseline to Month 24, with the alternative hypotheses that there was a difference.

The radiographic endpoints of nonprogression (TSS and erosion score changes ≤0.0, ≤0.5, ≤3.0, and <SDD) were analyzed using a Mantel-Haenszel approach. Erosion and JSN scores were analyzed as other radiographic endpoints using the same statistical approach as for TSS.

Inter- and intra-reader reliability correlation coefficients were determined. Inter-reader correlation coefficients were calculated based on the scoring of all Baseline images of all the cases read by both readers. ANOVA was used for the comparison of inter-reader variability. Intrareader correlation coefficients were calculated based on the scoring of all original Baseline images and a randomly selected sample of 30 reread images. Subgroup analysis for the primary radiographic efficacy endpoint was performed for subjects having a Baseline DAS 28 >5.1. The same ANCOVA model that was used for the primary analysis was used for the subgroup analysis, with terms added for the subgroup factor and subgroup × treatment group interaction.

No adjustment for multiple comparisons was made on any 2-year analyses (considered secondary). The p-values from these comparisons were considered descriptive.

## RESULTS

### Subject Disposition and Demography:

A total of 542 subjects were enrolled in the Period 1 (first year) of this study; of these, 268 subjects were randomized to the MTX treatment group and 274 subjects were randomized to the ETN + MTX treatment group. All 542 enrolled subjects received at least 1 dose of test article.

A total of 411 subjects were enrolled in the Period 2 (second year) of this study, and all of these subjects received at least 1 dose of test article during Year 2. Of these, 111 subjects were randomly assigned to the ETN+MTX/ETN+MTX treatment group, 90 subjects were randomly assigned to the MTX/MTX+ETN treatment group, 111 subjects were randomly assigned to the ETN+MTX/ETN treatment group, and 99 were randomly assigned to the MTX/MTX treatment group.

The total number of subjects who were randomly assigned in the Period 2 (second year) of the study and the number of subjects who were evaluable for radiographic efficacy are summarized by treatment group in Table 3. Fifty (50) of the 411 subjects (12.2%) who enrolled in this study were excluded from the radiographic ITT population. The radiographic ITT population included 361 subjects: 99 subjects in the ETN+MTX/ETN+MTX treatment group, 79 in the MTX/MTX+ETN treatment group, 99 in the ETN+MTX/ETN treatment group, and 84 in MTX/MTX treatment group.

**Table 3. Number of Subjects in the Analysis Populations, by Treatment Group**

| Population | ETN+MTX/ ETN+MTX | MTX/ ETN+MTX | ETN+MTX/ ETN | MTX/MTX | Total |
|---|---|---|---|---|---|
| Randomized | 111 | 90 | 111 | 99 | 411 |
| Evaluable for clinical efficacy (mITT population) | 108 | 88 | 108 | 94 | 398 |
| Evaluable for radiographic efficacy (radiographic ITT population) | 99 | 79 | 99 | 84 | 361 |

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

Demographic and other Baseline characteristics for the safety population during Period 1 are presented in Table 4.

**Table 4. Demographic and Other Characteristics, Safety Population (Baseline, Period 1)**

| Characteristic | Treatment Group | | Total (n=542) | Overall p-Value |
|---|---|---|---|---|
| | Methotrexate (n=268) | Etanercept + Methotrexate (n=274) | | |
| Age (years) | | | | |
| N | 268 | 274 | 542 | |
| Mean | 52.26 | 50.69 | 51.46 | 0.191[a] |
| Standard error | 0.80 | 0.89 | 0.60 | |
| Minimum | 20.00 | 18.00 | 18.00 | |
| Maximum | 84.00 | 82.00 | 84.00 | |
| Median | 51.50 | 52.50 | 52.00 | |
| Sex, n (%) | | | | 0.627[b] |
| Female | 194 (72.39) | 204 (74.45) | 398 (73.43) | |
| Male | 74 (27.61) | 70 (25.55) | 144 (26.57) | |

N = total number of subjects; n = number of subjects in sub-group.
a. One-way analysis of variance with treatment as factor.
b. Fisher's Exact Test (2-tailed).

Table 5 shows the demographic characteristics (Baseline, Period 2) for the radiographic ITT population at Week 52 by treatment group and overall.

**Table 5. Demographic and Other Baseline Characteristics, Radiographic ITT Population at Week 52 (Baseline, Period 2)**

| Characteristic | p-Value | Treatment | | | | |
|---|---|---|---|---|---|---|
| | | E+M/E+M (n=99) | M/M+E (n=79) | E+M/E (n=99) | M/M (n=84) | Total (n=361) |
| Age | | | | | | |
| N | | 99 | 79 | 99 | 84 | 361 |
| Mean | 0.610[a] | 52.83 | 55.06 | 52.50 | 53.71 | 53.43 |
| Standard deviation | | 14.10 | 12.93 | 14.38 | 12.84 | 13.62 |
| Minimum | | 23.74 | 26.04 | 19.11 | 26.55 | 19.11 |
| Maximum | | 82.77 | 83.08 | 79.16 | 78.97 | 83.08 |
| Median | | 53.33 | 56.93 | 55.42 | 52.59 | 54.65 |
| Sex | 0.003[b] | | | | | |
| Female | | 72 (72.73) | 46 (58.23) | 76 (76.77) | 70 (83.33) | 264 (73.13) |
| Male | | 27 (27.27) | 33 (41.77) | 23 (23.23) | 14 (16.67) | 97 (26.87) |

E = etanercept; M = methotrexate; N = total number of subjects; n = number of subjects in sub-group.
a. One-way analysis of variance with treatment as factor.
b. p-Value for Chi-Square.

Overall, 132 (24.4%) subjects were discontinued during the first year of the study; 79 (29.5%) of those subjects were in the MTX treatment group and 53 (19.3%) subjects were in the ETN + MTX treatment group (p=0.007; Table 6).

**Table 6. Number (%) of Subjects Who Were Discontinued, By Primary Reason**

| Reason[a] | Treatment Group | | Total | Overall |
|---|---|---|---|---|
| | Methotrexate (n=268) | Etanercept + Methotrexate (n=274) | (n=542) | p-Value[b] |
| Any reason | 79 (29.48) | 53 (19.34) | 132 (24.35) | 0.007 |
| Adverse event | 34 (12.69) | 27 (9.85) | 61 (11.25) | 0.342 |
| System toxicity[c] | 0 (0.00) | 1 (0.36) | 1 (0.18) | 1.000 |
| Lack of efficacy | 24 (8.96) | 9 (3.28) | 33 (6.09) | 0.007 |
| Lack of subject compliance with the protocol | 5 (1.87) | 1 (0.36) | 6 (1.11) | 0.119 |
| Lost to follow-up | 1 (0.37) | 0 (0.00) | 1 (0.18) | 0.494 |
| Missed >4 consecutive doses of test article | 3 (1.12) | 2 (0.73) | 5 (0.92) | 0.683 |
| Other | 2 (0.75) | 3 (1.09) | 5 (0.92) | 1.000 |
| Principal investigator decision | 1 (0.37) | 0 (0.00) | 1 (0.18) | 0.494 |
| Subject request to withdrawal | 8 (2.99) | 9 (3.28) | 17 (3.14) | 1.000 |
| Violation of inclusion/exclusion criteria | 1 (0.37) | 1 (0.36) | 2 (0.37) | 1.000 |

ALT = alanine aminotransferase; N = total number of subjects; n = number of subjects in sub-group.
a. Total discontinued (ie, any reason) is the sum of individual reasons because they are mutually exclusive by subject.
b. Fisher's Exact Test (2-tailed).
c. The system toxicity was an increased serum ALT of 136 IU/L (normal range, 0 to 48 IU/L).

Overall, 64 (15.57%) subjects were discontinued from the study during Week 52 to Week 104 of the study; 7 (6.31%) of those subjects were in the ETN+MTX/ETN+MTX treatment group, 16 (17.78%) were in the MTX/MTX+ETN treatment group, 18 (16.22%) were in the ETN+MTX/ETN treatment group, and 23 (23.23%) were in the MTX/MTX treatment group (p=0.004, Table 7). All subject discontinuations during Year 2 of the study are included in Table 7.

**Table 7. Number (%) of Subjects Who Discontinued by Primary Reason During Period 2 (Week 52 to Week 104)**

| Reasons[a] n (%) | Overall p-Value[b] | Treatment | | | | |
|---|---|---|---|---|---|---|
| | | E+M/ E+M N=111 | M/M+E N=90 | E+M/E N=111 | M/M N=99 | Total N=411 |
| Discontinued | 0.004** | 7 (6.31) | 16 (17.78) | 18 (16.22) | 23 (23.23) | 64 (15.57) |
| Adverse event | 0.169 | 3 (2.70) | 7 (7.78) | 5 (4.50) | 9 (9.09) | 24 (5.84) |
| Lack of efficacy | 0.003** | 0 | 1 (1.11) | 7 (6.31) | 7 (7.07) | 15 (3.65) |
| Lack of subject compliance with the protocol | 0.306 | 1 (0.90) | 0 | 0 | 2 (2.02) | 3 (0.73) |
| Lost to follow-up | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Missed >4 consecutive doses of test article | 0.894 | 1 (0.90) | 1 (1.11) | 1 (0.90) | 0 | 3 (0.73) |
| Other | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Principal investigator decision | 0.593 | 1 (0.90) | 1 (1.11) | 0 | 0 | 2 (0.49) |
| Subject request to withdrawal | 0.276 | 1 (0.90) | 5 (5.56) | 4 (3.60) | 3 (3.03) | 13 (3.16) |
| System toxicity | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

E = etanercept; M = methotrexate; n (%) = number of subjects with a given reason for discontinuation and percent of the total per number of subjects in each treatment group or number of total enrolled subjects); N = all enrolled subjects who discontinued during Period 1 per treatment group or per total enrolled.

a. Total discontinued is the sum of individual reasons because they are mutually exclusive by subjects.

b. Fisher exact test (2-tailed). Statistical significance at the .05, .01, and .001 levels is denoted by *, **, and ***, respectively.

## Efficacy Results:

The primary radiographic endpoint in this study was the change in modified TSS over 12 months.

The mean change in modified TSS from Week 0 to Week 52 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (p<0.001, ANCOVA; Table 8).

## Table 8. Mean (2-Sided 95% CI) Change in Modified Total Sharp Score From Week 0 to Week 52 ( LOCF)

| Time on Therapy | Treatment Group | N | Mean (SD) | Median (Q1, Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 2a Difference (95% CI) | Group 1a vs Group 2a p-Value | Group 1a vs Group 2b Difference (95% CI) | Group 1a vs Group 2b p-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week 52 | ETN+MTX/ETN+MTX | 99 | 0.35 (3.14) | 0.00 (0.00, 0.50) | -6.17 ~ 16.68 | 0.30 | (-0.28, 0.98) | -0.18 (-0.26,-0.10) | <0.001 | -0.12 (-0.20,-0.05) | 0.002 |
| | MTX/ETN+MTX | 79 | 2.56 (6.10) | 0.99 (0.00, 2.04) | -14.92 ~ 34.16 | <0.001 | (1.19, 3.93) | - | - | - | - |
| | ETN+MTX/ETN | 99 | 0.47 (2.53) | 0.00 (0.00, 0.50) | -6.00 ~ 19.45 | 0.16 | (-0.03, 0.98) | - | - | - | - |
| | MTX/MTX | 83 | 2.55 (6.41) | 0.00 (0.00, 1.77) | -1.50 ~ 28.84 | <0.001 | (1.15, 3.95) | - | - | - | - |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; n = number of subjects in sub-group; SD = standard deviation; vs = vesus.
a. p-Value for testing Rate = 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked Rate = Therapy+Country+Baseline Rank.

The mean change in modified TSS from Week 0 to Week 104 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group ($p<0.001$, ANCOVA; Table 9).

## Table 9. Mean (2-Sided 95% CI) Change in Modified Total Sharp Score From Week 0 to Week 104

| Time on Therapy | Treatment Group | N | Mean (SD) | Median (Q1, Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 2a | | Group 1a vs Group 2b | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Difference (95% CI) | p-Value | Difference (95% CI) | p-Value[b] |
| Week 104 | ETN+MTX/ ETN+MTX | 99 | 0.33 (3.22) | 0.00 (-0.48, 0.00) | -7.19 ~ 21.12 | 0.89 | (-0.32, 0.97) | -0.19 (-0.26, -0.11) | <0.001 | -0.18 (-0.25, -0.10) | <0.001 |
| | MTX/ETN+ MTX | 79 | 3.32 (8.83) | 1.00 (0.00, 3.05) | -15.65 ~ 41.42 | <0.001 | (1.34, 5.30) | - | - | - | - |
| | ETN+MTX/ ETN | 99 | 0.69 (3.79) | 0.00 (0.00, 0.53) | -17.97 ~ 25.55 | 0.011 | (-0.07, 1.44) | - | - | - | - |
| | MTX/MTX | 84 | 4.65 (12.84) | 0.51 (0.00, 2.93) | -2.50 ~ 71.33 | <0.001 | (1.86, 7.43) | - | - | - | - |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; n = number of subjects in sub-group; SD = standard deviation; vs = vesus.
a. p-Value for testing Rate=0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The mean change in modified TSS from Week 52 to Week 104 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (p=0.006, ANCOVA; Table 10).

## Table 10. Mean (2-Sided 95% CI) Change in Modified Total Sharp Score From Week 52 to Week 104 ( LOCF)

| Time on Therapy | Treatment Group | N | Mean (SD) | Median (Q1, Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 1b Difference (95% CI) | Group 1a vs Group 1b p-Value | Group 2a vs Group 2b Difference (95% CI) | Group 2a vs Group 2b p-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week 104 | ETN+MTX/ETN+MTX | 99 | -0.02 (1.52) | 0.00 (-0.05, 0.00) | -4.96 ~ 10.09 | 0.26 | (-0.32, 0.29) | -0.10 (-0.18, -0.03) | 0.006 | -0.06 (-0.15, 0.02) | 0.12 |
| | MTX/ETN+MTX | 79 | 0.78 (3.73) | 0.00 (-0.47, 0.50) | -8.19 ~ 21.67 | 0.23 | (-0.06, 1.61) | | | | |
| | ETN+MTX/ETN | 99 | 0.11 (3.27) | 0.00 (0.00, 0.50) | -28.08 ~ 8.27 | 0.042 | (-0.54, 0.77) | | | | |
| | MTX/MTX | 83 | 2.07 (7.55) | 0.00 (0.00, 0.98) | -9.24 ~ 44.95 | 0.024 | (0.42, 3.72) | | | | |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = number of subjects; SD = standard deviation; N = total number of subjects; n = number of subjects in sub-group; SD = standard deviation; vs = vesus.

a. p-Value for testing Rat e= 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The mean change in erosion score from Week 0 to Week 52 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group ($p<0.001$, ANCOVA; Table 11).
The mean change in erosion score from Week 0 to Week 104 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group ($p<0.001$, ANCOVA; Table 11).

## Table 11. Mean (2-Sided 95% CI) Change in Erosion Score From Week 0 to Weeks 52 and 104 (LOCF)

| Time on Therapy | Treatment Group | N | Mean (SD) | Median (Q1, Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 2a Difference (95% CI) | Group 1a vs Group 2a p-Value | Group 1a vs Group 2b Difference (95% CI) | Group 1a vs Group 2b p-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week 52 | ETN+MTX/ETN+MTX | 99 | 0.35 (2.61) | 0.00 (0.00, 0.00) | -6.17 ~ 16.68 | 0.28 | (-0.17, 0.87) | -0.20 (-0.28, -0.12) | <0.001 | -0.13 (-0.21, -0.05) | 0.001 |
| | MTX/ETN+MTX | 79 | 1.62 (3.43) | 0.98 (0.00, 2.00) | -10.94 ~ 16.55 | <0.001 | (0.85, 2.39) | | | | |
| | ETN+MTX/ETN | 99 | 0.24 (1.15) | 0.00 (0.00, 0.49) | -1.59 ~ 6.52 | 0.26 | (0.01, 0.47) | | | | |
| | MTX/MTX | 83 | 1.92 (5.10) | 0.00 (0.00, 1.00) | -1.00 ~ 26.00 | <0.001 | (0.81, 3.04) | | | | |
| Week 104 | ETN+MTX/ETN+MTX | 99 | 0.24 (2.26) | 0.00 (0.00, 0.00) | -6.47 ~ 11.11 | 0.80 | (-0.21, 0.69) | -0.18 (-0.26, -0.11) | <0.001 | -0.17 (-0.24, -0.09) | <0.001 |
| | MTX/ETN+MTX | 79 | 2.03 (4.98) | 0.50 (0.00, 2.08) | -12.30 ~ 23.60 | <0.001 | (0.91, 3.14) | | | | |
| | ETN+MTX/ETN | 99 | 0.26 (2.21) | 0.00 (0.00, 0.51) | -15.49 ~ 7.58 | 0.019 | (-0.18, 0.70) | | | | |
| | MTX/MTX | 84 | 3.31 (9.33) | 0.50 (0.00, 1.96) | -2.13 ~ 49.87 | <0.001 | (1.29, 5.34) | | | | |

Note: Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; SD = standard deviation; vs = versus.
a. p-Value for testing Rate = 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The mean change in erosion score from Week 52 to Week 104 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (p=0.015, ANCOVA; Table 12).

## Table 12. Mean (2-Sided 95% CI) Change in Erosion Score From Week 52 to Week 104 (LOCF)

| | | | | | | | | Group 1a vs Group 1b | | Group 2a vs Group 2b | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time on Therapy** | **Treatment Group** | **N** | **Mean (SD)** | **Median (Q1, Q3)** | **Min ~ Max** | **p-Value[a]** | **95% CI of Mean** | **Difference (95% CI)** | **p-Value** | **Difference (95% CI)** | **p-Value[b]** |
| Week 104 | ETN+MTX/ETN+MTX | 99 | -0.10 (0.93) | 0.00 (0.00, 0.00) | -5.15 ~ 3.36 | 0.33 | (-0.29, 0.08) | -0.09 (-0.16, -0.02) | 0.015 | -0.10 (-0.17, -0.02) | 0.017 |
| | MTX/ETN+MTX | 79 | 0.43 (2.28) | 0.00 (-0.47, 0.00) | -2.11 ~ 12.52 | 0.64 | (-0.08, 0.94) | | | | |
| | ETN+MTX/ETN | 99 | -0.06 (2.85) | 0.00 (0.00, 0.00) | -26.21 ~ 7.17 | 0.14 | (-0.63, 0.50) | | | | |
| | MTX/MTX | 83 | 1.35 (5.00) | 0.00 (0.00, 0.53) | -4.62 ~ 25.99 | 0.024 | (0.26, 2.44) | | | | |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; SD = standard deviation; vs = versus.
a. p-Value for testing Rate = 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The mean change in JSN score from Week 0 to Week 52 was not significantly different in the ETN+MTX/ETN+MTX treatment group compared with the MTX/ETN+MTX treatment group (p=0.16, ANCOVA; Table 13)

The mean change in JSN score from Week 0 to Week 104 was not significantly different in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (p=0.093, ANCOVA; Table 13).

**Table 13. : Mean (2-Sided 95% CI) Change in Joint Space Narrowing Score From Week 0 to Weeks 52 and 104 (LOCF)**

| | | | | | | | | Group 1a vs Group 2a | | Group 1a vs Group 2b | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time on Therapy** | **Treatment Group** | **N** | **Mean (SD)** | **Median (Q1, Q3)** | **Min ~ Max** | **p-Value[a]** | **95% CI of Mean** | **Difference (95% CI)** | **p-Value** | **Difference (95% CI)** | **p-Value[b]** |
| Week 52 | ETN+MTX/ETN+MTX | 99 | -0.00 (1.23) | 0.00 (0.00, 0.00) | -6.00 ~ 5.07 | 0.63 | (-0.25, 0.24) | -0.05 (-0.11, 0.02) | 0.16 | -0.06 (-0.13, 0.00) | 0.064 |
| | MTX/ETN+MTX | 79 | 0.94 (3.37) | 0.00 (0.00, 0.48) | -3.98 ~ 21.41 | 0.007 | (0.18, 1.69) | | | | |
| | ETN+MTX/ETN | 99 | 0.24 (1.88) | 0.00 (0.00, 0.00) | -4.50 ~ 15.46 | 0.32 | (-0.14, 0.61) | | | | |
| | MTX/MTX | 83 | 0.62 (1.91) | 0.00 (0.00, 0.44) | -1.50 ~ 11.54 | <0.001 | (0.21, 1.04) | | | | |
| Week 104 | ETN+MTX/ETN+MTX | 99 | 0.09 (1.54) | 0.00 (0.00, 0.00) | -6.07 ~ 10.81 | 0.78 | (-0.22, 0.39) | -0.06 (-0.13, 0.01) | 0.093 | -0.08 (-0.15, -0.02) | 0.016 |
| | MTX/ETN+MTX | 79 | 1.30 (4.55) | 0.00 (0.00, 0.52) | -3.35 ~ 26.30 | 0.006 | (0.28, 2.32) | | | | |
| | ETN+MTX/ETN | 99 | 0.43 (2.40) | 0.00 (0.00, 0.00) | -4.29 ~ 19.65 | 0.072 | (-0.05, 0.91) | | | | |
| | MTX/MTX | 84 | 1.33 (4.29) | 0.00 (0.00, 0.99) | -2.50 ~ 24.93 | <0.001 | (0.40, 2.26) | | | | |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects SD = standard deviation; vs = versus.
a. p-Value for testing Rate = 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The mean change in JSN score from Week 52 to Week 104 was not significantly different in the ETN+MTX/ETN+MTX treatment group compared with the MTX/ETN+MTX treatment group (p=0.17, ANCOVA; Table 14).

**Table 14: Mean (2-Sided 95% CI) Change in Joint Space Narrowing Score From Week 52 to Week 104 (LOCF)**

| Time on Therapy | Treatment Group | N | Mean (SD) | Median (Q1, Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 1b Difference (95% CI) | Group 1a vs Group 1b P-Value | Group 2a vs Group 2b Difference (95% CI) | Group 2a vs Group 2b P-Value[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week 104 | ETN+MTX/ETN+MTX | 99 | 0.08 (0.94) | 0.00 (0.00, 0.00) | -2.04 ~ 6.72 | 0.83 | (-0.10, 0.27) | -0.04 (-0.10, 0.02) | 0.17 | -0.00 (-0.07, 0.06) | 0.92 |
| | MTX/ETN+MTX | 79 | 0.35 (1.75) | 0.00 (0.00, 0.00) | -6.74 ~ 9.15 | 0.024 | (-0.05, 0.74) | - | - | - | - |
| | ETN+MTX/ETN | 99 | 0.18 (0.99) | 0.00 (0.00, 0.00) | -1.87 ~ 6.81 | 0.17 | (-0.02, 0.38) | - | - | - | - |
| | MTX/MTX | 83 | 0.72 (2.94) | 0.00 (0.00, 0.00) | -4.62 ~ 18.95 | 0.004 | (0.08, 1.36) | - | - | - | - |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ANCOVA = analysis of covariance; CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min = minimum; Max = maximum; MTX = methotrexate; N = total number of subjects; SD = standard deviation; vs = versus.
a. p-Value for testing Rate = 0 was obtained from Wilcoxon Signed-Rank Test.
b. ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank.

The number and percentage of subjects who had an annualized change from Week 0 to Week 52 in modified TSS of ≤0.0 are presented in Table 15.

**Table 15. Number (%) of Subjects Having an Annualized Change in Modified Total Sharp Score of ≤0.0 From Week 0 to Week 52 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=84) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 52 | 71/99 (71.7%) | 31/79 (39.2%) | 65/99 (65.7%) | 42/83 (50.6%) | 0.444 | 0.158 | 0.004 | <.001 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
CI = confidence interval; ETN = etanercept; LOCF = last observation carried forward; Min=minimum; Max=maximum; MTX=methotrexate; n = total number of subjects I sub group; N = total number of subjects.

The number and percentage of subjects who had an annualized change from Week 52 to Week 104 in modified TSS of ≤0.0 are presented in Table 16.

**Table 16. Number (%) of Subjects Having an Annualized Change in Modified Total Sharp Score of ≤0.0 From Week 52 to Week 104 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=83) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 104 | 86/99 (86.9%) | 58/79 (73.4%) | 70/99 (70.7%) | 48/83 (57.8%) | 0.009 | 0.047 | <.001 | 0.034 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from baseline ≤0.0; N = number of subjects with data; vs = versus.

The number and percentage of subjects who had an annualized change from Week 0 to Week 52 in modified TSS of ≤0.5 are presented in Table 17.

**Table 17. Number (%) of Subjects Having an Annualized Change in Modified Total Sharp Score Change From Week 0 to Week 52 ≤0.5 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=84) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 52 | 81/99 (81.8%) | 35/79 (44.3%) | 79/99 (79.8%) | 53/83 (63.9%) | 0.857 | 0.018 | 0.007 | <.001 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from Baseline ≤0.0; N = number of subjects with data; vs = versus.

The number and percentage of subjects who had an annualized change from Week 52 to Week 104 in modified TSS of ≤0.5 are presented in Table 18.

**Table 18. Number (%) of Subjects Having an Annualized Change in Modified Total Sharp Score of ≤0.5 From Week 52 to 104 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=83) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 104 | 89/99 (89.9%) | 59/79 (74.7%) | 74/99 (74.7%) | 56/83 (67.5%) | 0.008 | 0.387 | <.001 | 0.009 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from Baseline ≤0.0; n = number of subjects in sub groups; N = total number of subjects; vs = versus.

The number and percentage of subjects who had an annualized change from Week 0 to Week 52 in modified TSS of ≤3.0 are presented in Table 19.

**Table 19. Number (%) of Subjects Having an Annualized Change of ≤3.0 in Modified Total Sharp Score Change From Week 0 to Week 52 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=84) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 52 | 93/99 (93.9%) | 62/79 (78.5%) | 92/99 (92.9%) | 69/83 (83.1%) | >0.999 | 0.550 | 0.030 | 0.003 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from Baseline ≤0.0; N = number of subjects with data; vs = versus.

The number and percentage of subjects who had an annualized change from year 2 Baseline to year 2 (Week 52 to Week 104) in modified TSS of ≤3.0 are presented in Table 20.

**Table 20. Number (%) of Subjects Having an Annualized Change of ≤3.0 in Modified Total Sharp Score Change From Week 52 to Week 104 (LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=99) n/N (%) | MTX/ ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ ETN Group 1b (N=99) n/N (%) | MTX/ MTX Group 2b (N=83) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 104 | 97/99 (98.0%) | 72/79 (91.1%) | 94/99 (94.9%) | 70/83 (84.3%) | 0.445 | 0.235 | <.001 | 0.080 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from Baseline ≤0.0; N = number of subjects with data; vs = versus.

The number and percentage of subjects who had an annualized change from Week 0 to Weeks 52 and 104 in modified TSS less than the SDD, (SDD = 2.756 in this study) are presented in Table 21.

**Table 21. Number (%) of Subjects Having an Annualized Change in Modified Total Sharp Score Less Than the Smallest Detectable Difference From Week 0 to Week 52 (LOCF)**

| Time on Therapy | ETN+MTX/ETN+MTX Group 1a (N=99) n/N (%) | MTX/ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ETN Group 1b (N=99) n/N (%) | MTX/MTX Group 2b (N=84) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 52 | 93/99 (93.9%) | 62/79 (78.5%) | 92/99 (92.9%) | 69/83 (83.1%) | >0.999 | 0.550 | 0.030 | 0.003 |

Only subjects with Baseline and post baseline values included for on therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b=ETN+MTX/ETN
Group 2b = MTX/MTX
ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; n = number of subjects with a change from Baseline less than the smallest detectable difference; N = number of subjects with data; vs = versus.

The number and percentage of subjects who had an annualized change from Week 52 to Week 104 in modified TSS less than the SDD are presented in Table 22.

**Table 22. Number (%) of Subjects Having an Annualized Change in Modified Sharp Score Less Than the Smallest Detectable Difference From Week 52 to Week 104 (LOCF)**

| Time on Therapy | ETN+MTX/ETN+MTX Group 1a (N=99) n/N (%) | MTX/ETN+MTX Group 2a (N=79) n/N (%) | ETN+MTX/ETN Group 1b (N=99) n/N (%) | MTX/MTX Group 2b (N=83) n/N (%) | p-Value (Fisher 2-Sided) Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
|---|---|---|---|---|---|---|---|---|
| Week 104 | 95/99 (96.0%) | 73/79 (92.4%) | 93/99 (93.9%) | 67/83 (80.7%) | 0.747 | 0.039 | 0.001 | 0.342 |

only subjects with Baseline and post baseline values included for on therapy visits
ETN=etanercept; LOCF=last observation carried forward; MTX=methotrexate; N=number of subjects with data n=number of subjects with a change from Baseline less than the smallest detectable difference; vs = versus.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX

The achievement of DAS remission (DAS <1.6) at Week 52 was weakly correlated to the ≤0.5 and ≤3.0 levels of change from the Year 1 Baseline in modified TSS (Table 23).

The achievement of DAS 28 remission (DAS <2.6) at Week 52 was weakly correlated to the ≤3.0 level of change from the Year 1 Baseline in modified TSS. The achievement of DAS 28 low disease activity (DAS <3.2) at Week 104 was weakly correlated to the ≤3.0 level of change from the Year 1 Baseline in modified TSS. The achievement of DAS 28 remission (DAS <2.6) at Week 104 was weakly correlated to the ≤3.0 level of change from the Year 1 baseline in modified TSS.

**Table 23. Correlation Between Clinical Response and Radiographic Nonprogression Based on Week 0 to Weeks 52 and 104 (LOCF)**

| Clinical Response Measure | Change From Baseline in Total Sharp Score | | | | | |
|---|---|---|---|---|---|---|
| | ≤0.0 | | ≤0.5 | | ≤3.0 | |
| | KAPPA Estimate (ASE) | 2-sided p-Value | KAPPA Estimate (ASE) | 2-sided p-Value | KAPPA Estimate (ASE) | 2-sided p-Value |
| Week 52 | | | | | | |
| DAS remission (DAS <1.6) | 0.057 (0.05) | 0.26 | 0.122 (0.05) | 0.010 | 0.064 (0.03) | 0.046 |
| DAS 28 low-disease activity (DAS 28 <3.2) | 0.021 (0.05) | 0.68 | 0.074 (0.05) | 0.15 | 0.063 (0.04) | 0.12 |
| DAS 28 remission (DAS 28 <2.6) | 0.013 (0.05) | 0.80 | 0.079 (0.05) | 0.094 | 0.075 (0.03) | 0.021 |
| Week 104 | | | | | | |
| DAS remission (DAS <1.6) | 0.029 (0.05) | 0.58 | 0.043 (0.05) | 0.39 | 0.072 (0.04) | 0.068 |
| DAS 28 low-disease activity (DAS 28 <3.2) | 0.038 (0.05) | 0.46 | 0.051 (0.05) | 0.33 | 0.115 (0.05) | 0.012 |
| DAS 28 remission (DAS 28 <2.6) | -0.002 (0.05) | 0.97 | 0.032 (0.05) | 0.53 | 0.089 (0.04) | 0.021 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
ASE = asymptotic standard error; DAS = disease activity score; DAS 28 = disease activity score for 28 joints; LOCF=last observation carried forward.

The achievement of each category of clinical response was weakly correlated to each of the 3 levels of change from Week 52 to Week 104 in modified TSS (Table 24).

**Table 24. Correlation Between Clinical Response and Radiographic Nonprogression Based on Week 52 to Week 104 (LOCF)**

| Clinical Response Measure | Change from Baseline in Total Sharp Score | | | | | |
|---|---|---|---|---|---|---|
| | ≤0.0 | | ≤0.5 | | ≤3.0 | |
| | KAPPA Estimate (ASE) | 2-sided p-Value | KAPPA Estimate (ASE) | 2-sided p-Value | KAPPA Estimate (ASE) | 2-sided p-Value |
| Week 104 | | | | | | |
| DAS remission (DAS <1.6) | 0.126 (0.05) | 0.009 | 0.139 (0.04) | <0.001 | 0.077 (0.03) | 0.005 |
| DAS 28 low-disease activity (DAS 28 <3.2) | 0.062 (0.05) | 0.23 | 0.131 (0.05) | 0.005 | 0.105 (0.04) | 0.002 |
| DAS 28 remission (DAS 28 <2.6) | 0.095 (0.05) | 0.044 | 0.129 (0.04) | 0.001 | 0.089 (0.03) | <0.001 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
ASE = asymptotic standard error; DAS = disease activity score; DAS 28 = disease activity score for 28 joints; LOCF=last observation carried forward.

The mean change (standard deviation [SD]) in modified TSS from Year 1 Baseline to Year 2 for subjects having a Baseline DAS 28 >5.1 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/MTX treatment group (0.37 [3.22] versus 2.35 [5.91]; p=0.004, ANCOVA; Table 25) and in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (0.37 [3.22] versus 2.72 [6.37]; p<0.001) at Week 52. The mean change (SD) in modified TSS from year 1 Baseline to Year 2 for subjects having a Baseline DAS 28 >5.1 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/MTX treatment group (0.34 [3.30] versus 4.10 [11.21]; p<0.001, ANCOVA; Table 25) and in the ETN+MTX/ETN+MTX treatment group compared with subjects in the MTX/ETN+MTX treatment group (0.34 [3.30] versus 3.58 [9.22]; p<0.001) at Week 104.

**Table 25. Summary of TSS Change From Week 0 to Weeks 52 and 104 for Subjects With Week 0 DAS28 Score >5.1 (LOCF)**

| | | | | | | | | Group 1a vs Group 2a | | Group 1a vs Group 2b | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time on Therapy** | **Therapy Group** | **N** | **Mean (SD)** | **Median (Q1, Q3)** | **Min ~ Max** | **p-Value[a]** | **95% CI of Mean** | **Difference (95% CI)** | **p-Value** | **Difference (95% CI)** | **p-Value** |
| Week 52 | ETN+MTX/ETN+MTX | 94 | 0.37 (3.22) | 0.00 (0.00, 0.50) | -6.17 ~ 16.68 | 0.30 | (-0.29, 1.03) | -0.18 (-0.27, -0.10) | <0.001 | -0.12 (-0.21, -0.04) | 0.004 |
| | MTX/ETN+MTX | 72 | 2.72 (6.37) | 0.98 (0.00, 2.74) | -14.92 ~ 34.16 | <0.001 | (1.22, 4.22) | | | | |
| | ETN+MTX/ETN | 89 | 0.45 (2.62) | 0.00 (0.00,0.50) | -6.00 ~ 19.45 | 0.31 | (-0.10, 1.00) | | | | |
| | MTX/MTX | 77 | 2.35 (5.91) | 0.00 (0.00, 1.77) | -1.50 ~ 28.00 | <0.001 | (1.01, 3.69) | | | | |
| Week 104 | ETN+MTX/ETN+MTX | 94 | 0.34 (3.30) | 0.00 (-0.50, 0.00) | -7.19 ~ 21.12 | 0.89 | (-0.33, 1.02) | -0.19 (-0.27, -0.11) | <0.001 | -0.17 (-0.25, -0.09) | <0.001 |
| | MTX/ETN+MTX | 72 | 3.58 (9.22) | 1.00 (0.00, 3.58) | -15.65 ~ 41.42 | <0.001 | (1.41, 5.74) | | | | |
| | ETN+MTX/ETN | 89 | 0.67 (3.96) | 0.00 (0.00, 0.52) | -17.97 ~ 25.55 | 0.034 | (-0.16, 1.50) | | | | |
| | MTX/MTX | 78 | 4.10 (11.21) | 0.50 (0.00, 3.01) | -2.50 ~ 71.33 | <0.001 | (1.58, 6.63) | | | | |

*ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank
Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
CI = class interval; DAS = disease activity score; DAS 28 = disease activity score for 28 joints; ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; SD = standard deviation; vs = versus.
a. p-Value for testing rate =0 was obtained from Wilcoxon Signed-Rank Test.

The mean change (SD) in modified TSS from Year 2 Baseline to Year 2 (Week 52) for subjects having a Baseline DAS 28 >5.1 was significantly different in favor of subjects in the ETN+MTX/ETN+MTX treatment group compared with subjects in the ETN+MTX/ETN treatment group (-0.02 [1.56] versus 0.11 [3.44]; p=0.007, ANCOVA; Table 26) at Week 104.

**Table 26. Summary of Annualized TSS Rate (for Subjects With Year 1 Baseline DAS28 >5.1), Based on Year 2 Baseline (LOCF)**

| Time on Therapy | Therapy Group | N | Mean (SD) | Median (Q1,Q3) | Min ~ Max | p-Value[a] | 95% CI of Mean | Group 1a vs Group 1b Difference (95% CI) | Group 1a vs Group 1b p-Value* | Group 2a vs Group 2b Difference (95% CI) | Group 2a vs Group 2b p-Value* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week 104 | ETN+MTX/ETN+MTX | 94 | -0.02 (1.56) | 0.00 (-0.45,0.00) | -4.96 ~ 10.09 | 0.26 | (-0.34,0.30) | -0.11 (-0.19,-0.03) | 0.007 | -0.05 (-0.13,0.04) | 0.28 |
| | MTX/ETN+MTX | 72 | 0.87 (3.89) | 0.00 (-0.49,0.51) | -8.19 ~ 21.67 | 0.15 | (-0.04,1.79) | | | | |
| | ETN+MTX/ETN | 89 | 0.11 (3.44) | 0.00 (0.00,0.49) | -28.08 ~ 8.27 | 0.053 | (-0.61,0.84) | | | | |
| | MTX/MTX | 77 | 1.72 (6.52) | 0.00 (0.00,0.58) | -9.24 ~ 44.95 | 0.033 | (0.24,3.21) | | | | |

*ANCOVA Model (Except Baseline): Ranked rate = Therapy+Country+Baseline Rank
only subjects with Baseline and post baseline values included for on therapy visits
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
CI = class interval; DAS = disease activity score; DAS 28 = disease activity score for 28 joints; ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; SD = standard deviation; vs = versus.
a. p-Value for testing rate=0 was obtained from Wilcoxon Signed-Rank Test.

The primary clinical efficacy endpoint in this study was the proportion of subjects in DAS 28 remission (ie, DAS 28 <2.6) at Week 52 (last observation carried forward [LOCF]).

At the 52-week time point, the proportion of subjects who achieved DAS 28 remission was significantly greater in the ETN+MTX treatment group (Table 27).

**Table 27. Number (%) of Subjects Who Achieved DAS 28 Remission (DAS 28 <2.6; LOCF), Week 52**

| Time Point | Treatment Group | | Between-Group p-Value[a] |
|---|---|---|---|
| | Methotrexate n/N (%) | Etanercept+Methotrexate n/N (%) | |
| Week 52 | 73/263 (27.8) | 132/265 (49.8) | <0.001 |

DAS 28 = disease activity score for 28 joints; LOCF = last-observation-carried-forward; n = number of responders; N = number of subjects with response data.
a. Fisher's Exact Test (2-tailed).

The between-group analysis of LOCF results for number and percentage of subjects who achieved DAS 28 remission is presented, by treatment group and at all-time points, in Table 28.

**Table 28. Number (%) of Subjects Who Achieved DAS 28 Remission (DAS 28 <2.6; LOCF), All Time Points**

| Time Point | Treatment Group | | Between-Group P-Value[a] |
|---|---|---|---|
| | Methotrexate n / N (%) | Etanercept+Methotrexate n / N (%) | |
| Baseline | 0/263 (0.0) | 0/265 (0.0) | — |
| Week 2 | 1/252 (0.4) | 13/258 (5.0) | 0.002 |
| Week 4 | 3/262 (1.1) | 31/264 (11.7) | <0.001 |
| Week 8 | 9/262 (3.4) | 55/265 (20.8) | <0.001 |
| Week 12 | 29/263 (11.0) | 79/265 (29.8) | <0.001 |
| Week 16 | 38/263 (14.4) | 93/265 (35.1) | <0.001 |
| Week 20 | 49/263 (18.6) | 114/265 (43.0) | <0.001 |
| Week 24 | 62/263 (23.6) | 111/265 (41.9) | <0.001 |
| Week 36 | 64/263 (24.3) | 125/265 (47.2) | <0.001 |
| Week 52 | 73/263 (27.8) | 132/265 (49.8) | <0.001 |

DAS 28 = disease activity score for 28 joints; LOCF = last-observation-carried-forward; n = number of responders; N = number of subjects with response data.
a. Fisher's Exact Test (2-tailed).

The between-group analysis of LOCF results for number and percentage of subjects who achieved DAS 28 remission is presented, by treatment groups and at all time points in Table 29.

**Table 29. Number (%) of Subjects Who Achieved DAS 28 Remission (DAS 28 <2.6; LOCF)**

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=108) | MTX/ ETN+MTX Group 2a (N=88) | ETN+MTX/ ETN Group 1b (N=108) | MTX/ MTX Group 2b (N=94) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/107 (0.0%) | 0/88 (0.0%) | 0/108 (0.0%) | 0/94 (0.0%) | | | | |
| Week 2 | 8/106 (7.5%) | 0/84 (0.0%) | 3/103 (2.9%) | 0/90 (0.0%) | 0.215 | | 0.008 | 0.010 |
| Week 4 | 17/107 (15.9%) | 1/88 (1.1%) | 11/107 (10.3%) | 1/94 (1.1%) | 0.311 | >0.999 | <0.001 | <0.001 |
| Week 8 | 25/107 (23.4%) | 2/88 (2.3%) | 24/108 (22.2%) | 5/94 (5.3%) | 0.872 | 0.446 | <.0001 | <0.001 |
| Week 12 | 38/107 (35.5%) | 12/88 (13.6%) | 33/108 (30.6%) | 11/94 (11.7%) | 0.471 | 0.824 | <0.001 | <0.001 |
| Week 16 | 42/108 (38.9%) | 17/88 (19.3%) | 41/108 (38.0%) | 13/94 (13.8%) | >0.999 | 0.327 | <0.001 | 0.003 |
| Week 20 | 52/108 (48.1%) | 17/88 (19.3%) | 52/108 (48.1%) | 23/94 (24.5%) | >0.999 | 0.475 | <0.001 | <0.001 |
| Week 24 | 49/108 (45.4%) | 25/88 (28.4%) | 47/108 (43.5%) | 28/94 (29.8%) | 0.891 | 0.871 | 0.029 | 0.018 |
| Week 36 | 54/108 (50.0%) | 25/88 (28.4%) | 57/108 (52.8%) | 30/94 (31.9%) | 0.785 | 0.631 | 0.010 | 0.003 |
| Week 52 | 54/108 (50.0%) | 35/88 (39.8%) | 63/108 (58.3%) | 26/94 (27.7%) | 0.275 | 0.087 | 0.001 | 0.194 |
| Week 64 | 62/108 (57.4%) | 46/88 (52.3%) | 54/108 (50.0%) | 34/94 (36.2%) | 0.339 | 0.036 | 0.003 | 0.564 |
| Week 80 | 62/108 (57.4%) | 47/88 (53.4%) | 51/108 (47.2%) | 33/94 (35.1%) | 0.173 | 0.017 | 0.002 | 0.665 |
| Week 104 | 62/108 (57.4%) | 51/88 (58.0%) | 54/108 (50.0%) | 33/94 (35.1%) | 0.339 | 0.003 | 0.002 | >0.999 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX.
DAS 28 = disease activity score for 28 joints; ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

The between-group analysis of LOCF results for number and percentage of subjects having a Baseline DAS 28 >5.1 who achieved DAS 28 remission (ie, DAS <1.6) is presented, by treatment group and at all time points in Table 30.

**Table 30. Number (%) of Subjects Having a Baseline DAS 28 >5.1 Who Achieved DAS 28 Remission (LOCF)**

| Time on Therapy | ETN+MTX/ETN+MTX Group 1a (N=101) | MTX/ETN+MTX Group 2a (N=81) | ETN+MTX/ETN Group 1b (N=97) | MTX/MTX Group 2b (N=85) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/101 (0.0) | 0/81 (0.0) | 0/97 (0.0) | 0/85 (0.0) | | | | |
| Week 2 | 7/100 (7.0) | 0/77 (0.0) | 2/93 (2.2) | 0/82 (0.0) | 0.172 | | 0.017 | 0.019 |
| Week 4 | 14/101 (13.9) | 0/81 (0.0) | 9/96 (9.4) | 0/85 (0.0) | 0.379 | | <0.001 | <0.001 |
| Week 8 | 22/101 (21.8) | 2/81 (2.5) | 20/97 (20.6) | 4/85 (4.7) | 0.864 | 0.682 | 0.001 | <0.001 |
| Week 12 | 34/101 (33.7) | 12/81 (14.8) | 30/97 (30.9) | 8/85 (9.4) | 0.762 | 0.344 | <0.001 | 0.004 |
| Week 16 | 38/101 (37.6) | 17/81 (21.0) | 36/97 (37.1) | 10/85 (11.8) | >0.999 | 0.141 | <0.001 | 0.023 |
| Week 20 | 48/101 (47.5) | 16/81 (19.8) | 47/97 (48.5) | 19/85 (22.4) | >0.999 | 0.708 | <0.001 | <0.001 |
| Week 24 | 45/101 (44.6) | 23/81 (28.4) | 40/97 (41.2) | 25/85 (29.4) | 0.668 | >0.999 | 0.048 | 0.031 |
| Week 36 | 49/101 (48.5) | 21/81 (25.9) | 49/97 (50.5) | 27/85 (31.8) | 0.887 | 0.494 | 0.025 | 0.002 |
| Week 52 | 48/101 (47.5) | 29/81 (35.8) | 57/97 (58.8) | 24/85 (28.2) | 0.120 | 0.321 | 0.010 | 0.132 |
| Week 64 | 56/101 (55.4) | 41/81 (50.6) | 49/97 (50.5) | 29/85 (34.1) | 0.569 | 0.041 | 0.005 | 0.552 |
| Week 80 | 56/101 (55.4) | 42/81 (51.9) | 47/97 (48.5) | 30/85 (35.3) | 0.393 | 0.042 | 0.008 | 0.656 |
| Week 104 | 57/101 (56.4) | 46/81 (56.8) | 48/97 (49.5) | 32/85 (37.6) | 0.393 | 0.019 | 0.012 | >0.999 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
DAS 28 = disease activity score for 28 joints; ETN = etanercept; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

The between-group analysis of LOCF results for number and percentage of subjects achieving a moderate or good response as defined by European league against rheumatism (EULAR) using DAS 28 criteria is presented, by treatment groups and at all time points, in Table 31.

## Table 31. Number (%) of Subjects Who Achieved DAS 28 EULAR Moderate or Good Response (LOCF)

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=107) | MTX/ ETN+MTX Group 2a (N=88) | ETN+MTX/ ETN Group 1b (N=108) | MTX/ MTX Group 2b (N=94) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/107 (0.0%) | 0/88 (0.0%) | 0/108 (0.0%) | 0/94 (0.0%) | | | | |
| Week 2 | 71/106 (67.0%) | 17/84 (20.2%) | 70/103 (68.0%) | 19/90 (21.1%) | 0.884 | >0.999 | <0.001 | <0.001 |
| Week 4 | 88/107 (82.2%) | 34/88 (38.6%) | 83/107 (77.6%) | 38/94 (40.4%) | 0.495 | 0.880 | <0.001 | <0.001 |
| Week 8 | 95/107 (88.8%) | 57/88 (64.8%) | 99/108 (91.7%) | 51/94 (54.3%) | 0.501 | 0.175 | <0.001 | <0.001 |
| Week 12 | 101/107 (94.4%) | 68/88 (77.3%) | 104/108 (96.3%) | 71/94 (75.5%) | 0.538 | 0.862 | <0.001 | <0.001 |
| Week 16 | 103/107 (96.3%) | 78/88 (88.6%) | 103/108 (95.4%) | 83/94 (88.3%) | >0.999 | >0.999 | 0.057 | 0.052 |
| Week 20 | 105/107 (98.1%) | 80/88 (90.9%) | 107/108 (99.1%) | 84/94 (89.4%) | 0.621 | 0.807 | 0.014 | 0.045 |
| Week 24 | 103/107 (96.3%) | 79/88 (89.8%) | 104/108 (96.3%) | 86/94 (91.5%) | >0.999 | 0.801 | 0.233 | 0.087 |
| Week 36 | 103/107 (96.3%) | 80/88 (90.9%) | 106/108 (98.1%) | 86/94 (91.5%) | 0.445 | >0.999 | 0.233 | 0.143 |
| Week 52 | 103/107 (96.3%) | 80/88 (90.9%) | 104/108 (96.3%) | 84/94 (89.4%) | >0.999 | 0.807 | 0.093 | 0.143 |
| Week 64 | 104/107 (97.2%) | 83/88 (94.3%) | 104/108 (96.3%) | 86/94 (91.5%) | >0.999 | 0.570 | 0.118 | 0.471 |
| Week 80 | 104/107 (97.2%) | 84/88 (95.5%) | 102/108 (94.4%) | 88/94 (93.6%) | 0.498 | 0.748 | 0.309 | 0.703 |
| Week 104 | 105/107 (98.1%) | 84/88 (95.5%) | 100/108 (92.6%) | 82/94 (87.2%) | 0.101 | 0.067 | 0.004 | 0.412 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
DAS 28 = disease activity score for 28 joints; ETN = etanercept; EULAR = European league against rheumatism; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

The between-group analysis of LOCF results for number and percentage of subjects achieving a good response as defined by EULAR using DAS 28 criteria is presented, by treatment groups and at all time points, in Table 32.

## Table 32. Number (%) of Subjects Who Achieved DAS 28 EULAR Good Response (LOCF)

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=107) | MTX/ ETN+MTX Group 2a (N=88) | ETN+MTX/ ETN Group 1b (N=108) | MTX/ MTX Group 2b (N=94) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/107 (0.0%) | 0/88 (0.0%) | 0/108 (0.0%) | 0/94 (0.0%) | | | | |
| Week 2 | 15/106 (14.2%) | 2/84 (2.4%) | 8/103 (7.8%) | 1/90 (1.1%) | 0.185 | 0.610 | <0.001 | 0.004 |
| Week 4 | 29/107 (27.1%) | 2/88 (2.3%) | 16/107 (15.0%) | 7/94 (7.4%) | 0.043 | 0.171 | <0.001 | <0.001 |
| Week 8 | 41/107 (38.3%) | 10/88 (11.4%) | 35/108 (32.4%) | 7/94 (7.4%) | 0.394 | 0.448 | <0.001 | <0.001 |
| Week 12 | 55/107 (51.4%) | 22/88 (25.0%) | 47/108 (43.5%) | 20/94 (21.3%) | 0.276 | 0.600 | <0.001 | <0.001 |
| Week 16 | 60/107 (56.1%) | 26/88 (29.5%) | 60/108 (55.6%) | 24/94 (25.5%) | >0.999 | 0.619 | <0.001 | <0.001 |
| Week 20 | 65/107 (60.7%) | 33/88 (37.5%) | 66/108 (61.1%) | 36/94 (38.3%) | >0.999 | >0.999 | 0.002 | 0.002 |
| Week 24 | 68/107 (63.6%) | 41/88 (46.6%) | 65/108 (60.2%) | 40/94 (42.6%) | 0.674 | 0.655 | 0.003 | 0.021 |
| Week 36 | 72/107 (67.3%) | 37/88 (42.0%) | 75/108 (69.4%) | 44/94 (46.8%) | 0.771 | 0.553 | 0.004 | <0.001 |
| Week 52 | 68/107 (63.6%) | 47/88 (53.4%) | 76/108 (70.4%) | 46/94 (48.9%) | 0.312 | 0.557 | 0.046 | 0.188 |
| Week 64 | 70/107 (65.4%) | 60/88 (68.2%) | 71/108 (65.7%) | 48/94 (51.1%) | >0.999 | 0.024 | 0.045 | 0.761 |
| Week 80 | 70/107 (65.4%) | 60/88 (68.2%) | 69/108 (63.9%) | 49/94 (52.1%) | 0.887 | 0.034 | 0.063 | 0.761 |
| Week 104 | 72/107 (67.3%) | 61/88 (69.3%) | 70/108 (64.8%) | 49/94 (52.1%) | 0.774 | 0.023 | 0.031 | 0.877 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
DAS 28 = disease activity score for 28 joints; ETN = etanercept; EULAR = European league against rheumatism; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

The between-group analysis of LOCF results for number and percentage of subjects achieving a moderate or good response as defined by EULAR using DAS criteria is presented, by treatment groups and at all time points, in Table 33.

## Table 33. Number (%) of Subjects Who Achieved DAS EULAR Moderate or Good Response (LOCF)

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=107) | MTX/ ETN+MTX Group 2a (N=88) | ETN+MTX/ ETN Group 1b (N=108) | MTX/ MTX Group 2b (N=94) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/107 (0.0%) | 0/88 (0.0%) | 0/108 (0.0%) | 0/94 (0.0%) | | | | |
| Week 2 | 73/106 (68.9%) | 17/84 (20.2%) | 68/103 (66.0%) | 23/90 (25.6%) | 0.768 | 0.472 | <0.001 | <0.001 |
| Week 4 | 93/107 (86.9%) | 37/88 (42.0%) | 76/107 (71.0%) | 39/94 (41.5%) | 0.007 | >0.999 | <0.001 | <0.001 |
| Week 8 | 98/107 (91.6%) | 60/88 (68.2%) | 94/108 (87.0%) | 55/94 (58.5%) | 0.378 | 0.219 | <0.001 | <0.001 |
| Week 12 | 103/107 (96.3%) | 71/88 (80.7%) | 101/108 (93.5%) | 76/94 (80.9%) | 0.538 | >0.999 | <0.001 | <0.001 |
| Week 16 | 104/107 (97.2%) | 80/88 (90.9%) | 103/108 (95.4%) | 85/94 (90.4%) | 0.721 | >0.999 | 0.070 | 0.068 |
| Week 20 | 104/107 (97.2%) | 83/88 (94.3%) | 106/108 (98.1%) | 86/94 (91.5%) | 0.683 | 0.570 | 0.118 | 0.471 |
| Week 24 | 105/107 (98.1%) | 79/88 (89.8%) | 105/108 (97.2%) | 86/94 (91.5%) | >0.999 | 0.801 | 0.048 | 0.025 |
| Week 36 | 105/107 (98.1%) | 80/88 (90.9%) | 106/108 (98.1%) | 87/94 (92.6%) | >0.999 | 0.790 | 0.086 | 0.045 |
| Week 52 | 105/107 (98.1%) | 79/88 (89.8%) | 106/108 (98.1%) | 85/94 (90.4%) | >0.999 | >0.999 | 0.026 | 0.025 |
| Week 64 | 104/107 (97.2%) | 85/88 (96.6%) | 103/108 (95.4%) | 87/94 (92.6%) | 0.721 | 0.333 | 0.194 | >0.999 |
| Week 80 | 102/107 (95.3%) | 86/88 (97.7%) | 102/108 (94.4%) | 89/94 (94.7%) | >0.999 | 0.446 | >0.999 | 0.461 |
| Week 104 | 104/107 (97.2%) | 86/88 (97.7%) | 99/108 (91.7%) | 80/94 (85.1%) | 0.135 | 0.003 | 0.004 | >0.999 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
DAS 28 = disease activity score for 28 joints; ETN = etanercept; EULAR = European league against rheumatism; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

The between-group analysis of LOCF results for number and percentage of subjects achieving a good response as defined by EULAR using DAS criteria is presented, by treatment groups and at all time points, in Table 34.

## Table 34. Number (%) of Subjects Who Achieved DAS EULAR Good Response (LOCF)

| Time on Therapy | ETN+MTX/ ETN+MTX Group 1a (N=107) | MTX/ ETN+MTX Group 2a (N=88) | ETN+MTX/ ETN Group 1b (N=108) | MTX/ MTX Group 2b (N=94) | p-Value (Fisher 2-Sided) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Group 1a vs Group 1b | Group 2a vs Group 2b | Group 1a vs Group 2b | Group 1a vs Group 2a |
| Baseline | 0/107 (0.0%) | 0/88 (0.0%) | 0/108 (0.0%) | 0/94 (0.0%) | | | | |
| Week 2 | 21/106 (19.8%) | 2/84 (2.4%) | 14/103 (13.6%) | 4/90 (4.4%) | 0.268 | 0.683 | 0.001 | <0.001 |
| Week 4 | 32/107 (29.9%) | 5/88 (5.7%) | 23/107 (21.5%) | 6/94 (6.4%) | 0.211 | >0.999 | <0.001 | <0.001 |
| Week 8 | 52/107 (48.6%) | 15/88 (17.0%) | 48/108 (44.4%) | 15/94 (16.0%) | 0.586 | 0.845 | <0.001 | <0.001 |
| Week 12 | 58/107 (54.2%) | 30/88 (34.1%) | 60/108 (55.6%) | 27/94 (28.7%) | 0.891 | 0.523 | <0.001 | 0.006 |
| Week 16 | 74/107 (69.2%) | 31/88 (35.2%) | 68/108 (63.0%) | 33/94 (35.1%) | 0.388 | >0.999 | <0.001 | <0.001 |
| Week 20 | 73/107 (68.2%) | 38/88 (43.2%) | 78/108 (72.2%) | 46/94 (48.9%) | 0.553 | 0.460 | 0.006 | <0.001 |
| Week 24 | 74/107 (69.2%) | 46/88 (52.3%) | 75/108 (69.4%) | 50/94 (53.2%) | >0.999 | >0.999 | 0.029 | 0.018 |
| Week 36 | 86/107 (80.4%) | 51/88 (58.0%) | 87/108 (80.6%) | 58/94 (61.7%) | >0.999 | 0.651 | 0.005 | <0.001 |
| Week 52 | 80/107 (74.8%) | 49/88 (55.7%) | 83/108 (76.9%) | 57/94 (60.6%) | 0.752 | 0.549 | 0.035 | 0.006 |
| Week 64 | 81/107 (75.7%) | 65/88 (73.9%) | 79/108 (73.1%) | 53/94 (56.4%) | 0.755 | 0.019 | 0.004 | 0.868 |
| Week 80 | 85/107 (79.4%) | 69/88 (78.4%) | 75/108 (69.4%) | 57/94 (60.6%) | 0.118 | 0.010 | 0.005 | 0.862 |
| Week 104 | 86/107 (80.4%) | 67/88 (76.1%) | 76/108 (70.4%) | 54/94 (57.4%) | 0.113 | 0.008 | <0.001 | 0.489 |

Only subjects with Baseline and postbaseline values were included for on-therapy visits.
Group 1a = ETN+MTX/ETN+MTX
Group 2a = MTX/ETN+MTX
Group 1b = ETN+MTX/ETN
Group 2b = MTX/MTX
DAS 28 = disease activity score for 28 joints; ETN = etanercept; EULAR = European league against rheumatism; LOCF = last observation carried forward; MTX = methotrexate; N = total number of subjects; vs = versus.

**Safety Results:**

The number and percentage of subjects reporting treatment emergent adverse events (TEAEs) with a frequency ≥ 5% in the 2 treatment groups for the first 12 months of the study, (from Baseline to Week 52) are summarized in Table 35.

Treatment-Emergent Adverse Events:

**Table 35. Treatment-Emergent Adverse Events Reported at a Frequency ≥5%-Number (%) of Subjects (from Baseline to Week 52)**

| System Organ Class[a] Preferred Term | Treatment Group | | |
|---|---|---|---|
| | Methotrexate N=268 | Etanercept + Methotrexate N=274 | Total N=542 |
| Any TEAE | 241 (89.93) | 246 (89.78) | 487 (89.85) |
| Gastrointestinal disorders | 126 (47.01) | 116 (42.34) | 242 (44.65) |
| Abdominal pain upper | 27 (10.07) | 23 (8.39) | 50 (9.23) |
| Diarrhoea | 20 (7.46) | 24 (8.76) | 44 (8.12) |
| Nausea | 48 (17.91) | 53 (19.34) | 101 (18.63) |
| Vomiting | 18 (6.72) | 11 (4.01) | 29 (5.35) |
| Infections and infestations | 127 (47.39) | 147 (53.65) | 274 (50.55) |
| Nasopharyngitis | 42 (15.67) | 44 (16.06) | 86 (15.87) |
| Upper respiratory tract infection | 19 (7.09) | 18 (6.57) | 37 (6.83) |
| Urinary tract infection | 10 (3.73) | 17 (6.20) | 27 (4.98) |
| Injury, poisoning and procedural complications | 50 (18.66) | 53 (19.34) | 103 (19.00) |
| Post procedural nausea | 23 (8.58) | 18 (6.57) | 41 (7.56) |
| Musculoskeletal and connective tissue disorders | 94 (35.07) | 69 (25.18) | 163 (30.07) |
| Rheumatoid arthritis | 36 (13.43) | 13 (4.74) | 49 (9.04) |
| Nervous system disorders | 49 (18.28) | 68 (24.82) | 117 (21.59) |
| Headache | 20 (7.46) | 29 (10.58) | 49 (9.04) |
| Respiratory, thoracic and mediastinal disorders | 49 (18.28) | 53 (19.34) | 102 (18.82) |
| Cough | 26 (9.70) | 23 (8.39) | 49 (9.04) |
| Skin and subcutaneous tissue disorders | 50 (18.66) | 73 (26.64) | 123 (22.69) |
| Alopecia | 8 (2.99) | 15 (5.47) | 23 (4.24) |
| Rash | 14 (5.22) | 16 (5.84) | 30 (5.54) |
| Vascular disorders | 30 (11.19) | 33 (12.04) | 63 (11.62) |
| Hypertension | 22 (8.21) | 17 (6.20) | 39 (7.20) |

AE/SAE results are not separated out.
TEAE = treatment-emergent adverse event; N = total number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same system organ class.

The number and percentage of subjects reporting TEAEs with a frequency ≥5% in the 4 treatment groups, for Second year of the study (Week 52 to Week 104,) are summarized in Table 36.

**Table 36. Treatment-Emergent Adverse Events Reported at a Frequency ≥5%-Number (%) of Subjects (Week 52 to Week 104)**

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Any adverse event | 0.955 | 91 (81.98) | 71 (78.89) | 89 (80.18) | 79 (79.80) | 330 (80.29) |
| Gastrointestinal disorders | 0.295 | 24 (21.62) | 23 (25.56) | 19 (17.12) | 27 (27.27) | 93 (22.63) |
| Diarrhoea | 0.412 | 4 (3.60) | 2 (2.22) | 6 (5.41) | 7 (7.07) | 19 (4.62) |
| Dyspepsia | 0.084 | 1 (0.90) | 0 | 3 (2.70) | 5 (5.05) | 9 (2.19) |
| Nausea | 0.413 | 8 (7.21) | 8 (8.89) | 4 (3.60) | 8 (8.08) | 28 (6.81) |
| General disorders and administration site conditions | 0.545 | 12 (10.81) | 14 (15.56) | 10 (9.01) | 11 (11.11) | 47 (11.44) |
| Infections and infestations | 0.748 | 47 (42.34) | 33 (36.67) | 49 (44.14) | 42 (42.42) | 171 (41.61) |
| Gastroenteritis | 0.040* | 7 (6.31) | 1 (1.11) | 1 (0.90) | 1 (1.01) | 10 (2.43) |
| Lower respiratory tract infection | 0.375 | 2 (1.80) | 1 (1.11) | 4 (3.60) | 5 (5.05) | 12 (2.92) |
| Nasopharyngitis | 0.720 | 10 (9.01) | 10 (11.11) | 10 (9.01) | 13 (13.13) | 43 (10.46) |
| Rhinitis | 0.275 | 2 (1.80) | 2 (2.22) | 6 (5.41) | 1 (1.01) | 11 (2.68) |
| Upper respiratory tract infection | 0.440 | 6 (5.41) | 8 (8.89) | 5 (4.50) | 9 (9.09) | 28 (6.81) |
| Urinary tract infection | 0.054 | 0 | 2 (2.22) | 6 (5.41) | 4 (4.04) | 12 (2.92) |
| Investigations | 0.046* | 20 (18.02) | 14 (15.56) | 7 (6.31) | 14 (14.14) | 55 (13.38) |
| Alanine aminotransferase increased | 0.067 | 5 (4.50) | 7 (7.78) | 2 (1.80) | 1 (1.01) | 15 (3.65) |
| Musculoskeletal and connective tissue disorders | 0.118 | 22 (19.82) | 20 (22.22) | 20 (18.02) | 31 (31.31) | 93 (22.63) |
| Back pain | 0.465 | 2 (1.80) | 3 (3.33) | 4 (3.60) | 6 (6.06) | 15 (3.65) |
| Rheumatoid arthritis | 0.016* | 6 (5.41) | 6 (6.67) | 4 (3.60) | 15 (15.15) | 31 (7.54) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.007** | 0 | 7 (7.78) | 2 (1.80) | 3 (3.03) | 12 (2.92) |
| Nervous system disorders | 0.517 | 10 (9.01) | 12 (13.33) | 17 (15.32) | 11 (11.11) | 50 (12.17) |
| Headache | 0.782 | 8 (7.21) | 4 (4.44) | 6 (5.41) | 4 (4.04) | 22 (5.35) |
| Psychiatric disorders | 0.035* | 4 (3.60) | 10 (11.11) | 4 (3.60) | 2 (2.02) | 20 (4.87) |
| Depression | 0.003** | 1 (0.90) | 5 (5.56) | 0 | 0 | 6 (1.46) |
| Respiratory, thoracic, and mediastinal disorders | 0.596 | 19 (17.12) | 10 (11.11) | 13 (11.71) | 13 (13.13) | 55 (13.38) |
| Cough | 0.429 | 7 (6.31) | 2 (2.22) | 8 (7.21) | 6 (6.06) | 23 (5.60) |
| Skin and subcutaneous tissue disorders | 0.455 | 17 (15.32) | 17 (18.89) | 14 (12.61) | 11 (11.11) | 59 (14.36) |
| Rash | 0.761 | 4 (3.60) | 5 (5.56) | 3 (2.70) | 4 (4.04) | 16 (3.89) |
| Vascular disorders | 0.668 | 7 (6.31) | 3 (3.33) | 5 (4.50) | 7 (7.07) | 22 (5.35) |

**Table 36. Treatment-Emergent Adverse Events Reported at a Frequency ≥5%-Number (%) of Subjects (Week 52 to Week 104)**

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Hypertension | 0.084 | 5 (4.50) | 0 | 3 (2.70) | 6 (6.06) | 14 (3.41) |

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Adverse events with a start date greater than or equal to the Visit 13 date was tabulated in this report.
E = etanercept; M = methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sub group.
a. Totals at a higher level are not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher level category.
b. Overall p-Value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by*, ** and *** respectively.

The number and percentage of subjects reporting TEAEs with a frequency ≥ 5% in the 4 treatment groups (Week 0 to Week 104) are summarized in Table 37.

## Table 37. Treatment-Emergent Adverse Events Reported at a Frequency ≥5% - Number (%) of Subjects (Week 0 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Any adverse event | 0.845 | 107 (96.40) | 85 (94.44) | 106 (95.50) | 93 (93.94) | 391 (95.13) |
| Blood and lymphatic system disorders | 0.013* | 15 (13.51) | 2 (2.22) | 11 (9.91) | 5 (5.05) | 33 (8.03) |
| Anaemia | 0.101 | 7 (6.31) | 1 (1.11) | 5 (4.50) | 1 (1.01) | 14 (3.41) |
| Lymphadenopathy | 0.096 | 6 (5.41) | 0 | 2 (1.80) | 2 (2.02) | 10 (2.43) |
| Eye disorders | 0.881 | 13 (11.71) | 9 (10.00) | 15 (13.51) | 13 (13.13) | 50 (12.17) |
| Dry eye | 0.252 | 1 (0.90) | 1 (1.11) | 2 (1.80) | 5 (5.05) | 9 (2.19) |
| Gastrointestinal disorders | 0.867 | 60 (54.05) | 51 (56.67) | 58 (52.25) | 57 (57.58) | 226 (54.99) |
| Abdominal pain | 0.780 | 4 (3.60) | 2 (2.22) | 5 (4.50) | 5 (5.05) | 16 (3.89) |
| Abdominal pain upper | 0.527 | 9 (8.11) | 10 (11.11) | 16 (14.41) | 11 (11.11) | 46 (11.19) |
| Constipation | 0.696 | 3 (2.70) | 2 (2.22) | 5 (4.50) | 5 (5.05) | 15 (3.65) |
| Diarrhoea | 0.472 | 12 (10.81) | 7 (7.78) | 12 (10.81) | 15 (15.15) | 46 (11.19) |
| Dyspepsia | 0.827 | 5 (4.50) | 4 (4.44) | 7 (6.31) | 7 (7.07) | 23 (5.60) |
| Mouth ulceration | 0.729 | 6 (5.41) | 2 (2.22) | 5 (4.50) | 5 (5.05) | 18 (4.38) |
| Nausea | 0.770 | 26 (23.42) | 20 (22.22) | 26 (23.42) | 28 (28.28) | 100 (24.33) |
| Vomiting | 0.334 | 6 (5.41) | 8 (8.89) | 5 (4.50) | 10 (10.10) | 29 (7.06) |
| General disorders and administration site conditions | 0.735 | 33 (29.73) | 22 (24.44) | 35 (31.53) | 29 (29.29) | 119 (28.95) |
| Asthenia | 0.776 | 7 (6.31) | 3 (3.33) | 5 (4.50) | 6 (6.06) | 21 (5.11) |
| Fatigue | 0.839 | 5 (4.50) | 4 (4.44) | 8 (7.21) | 5 (5.05) | 22 (5.35) |
| Injection site reaction | 0.170 | 2 (1.80) | 1 (1.11) | 7 (6.31) | 2 (2.02) | 12 (2.92) |
| Oedema peripheral | 0.585 | 4 (3.60) | 2 (2.22) | 2 (1.80) | 5 (5.05) | 13 (3.16) |
| Immune system disorders | 0.144 | 3 (2.70) | 1 (1.11) | 8 (7.21) | 3 (3.03) | 15 (3.65) |
| Infections and infestations | 0.644 | 77 (69.37) | 56 (62.22) | 76 (68.47) | 63 (63.64) | 272 (66.18) |
| Bronchitis | 0.641 | 9 (8.11) | 4 (4.44) | 6 (5.41) | 8 (8.08) | 27 (6.57) |
| Gastroenteritis | 0.100 | 10 (9.01) | 4 (4.44) | 2 (1.80) | 4 (4.04) | 20 (4.87) |
| Herpes simplex | 0.277 | 6 (5.41) | 1 (1.11) | 7 (6.31) | 4 (4.04) | 18 (4.38) |
| Herpes zoster | 0.073 | 0 | 3 (3.33) | 2 (1.80) | 5 (5.05) | 10 (2.43) |
| Influenza | 0.788 | 7 (6.31) | 3 (3.33) | 7 (6.31) | 5 (5.05) | 22 (5.35) |
| Lower respiratory tract infection | 0.376 | 4 (3.60) | 5 (5.56) | 5 (4.50) | 9 (9.09) | 23 (5.60) |
| Nasopharyngitis | 0.781 | 24 (21.62) | 20 (22.22) | 27 (24.32) | 27 (27.27) | 98 (23.84) |
| Pharyngitis | 0.023* | 10 (9.01) | 2 (2.22) | 7 (6.31) | 1 (1.01) | 20 (4.87) |
| Rhinitis | 0.879 | 7 (6.31) | 4 (4.44) | 8 (7.21) | 7 (7.07) | 26 (6.33) |
| Sinusitis | 0.803 | 4 (3.60) | 2 (2.22) | 4 (3.60) | 5 (5.05) | 15 (3.65) |
| Injury, poisoning and procedural complications | 0.875 | 28 (25.23) | 25 (27.78) | 32 (28.83) | 24 (24.24) | 109 (26.52) |
| Postprocedural nausea | 0.596 | 8 (7.21) | 10 (11.11) | 8 (7.21) | 11 (11.11) | 37 (9.00) |
| Investigations | 0.271 | 31 (27.93) | 28 (31.11) | 22 (19.82) | 28 (28.28) | 109 (26.52) |
| Alanine aminotransferase increased | 0.375 | 6 (5.41) | 10 (11.11) | 6 (5.41) | 6 (6.06) | 28 (6.81) |
| Hepatic enzyme increased | 0.312 | 5 (4.50) | 4 (4.44) | 2 (1.80) | 7 (7.07) | 18 (4.38) |
| Musculoskeletal and connective tissue disorders | 0.116 | 43 (38.74) | 33 (36.67) | 36 (32.43) | 48 (48.48) | 160 (38.93) |
| Arthralgia | 0.893 | 7 (6.31) | 6 (6.67) | 10 (9.01) | 7 (7.07) | 30 (7.30) |
| Back pain | 0.484 | 5 (4.50) | 4 (4.44) | 8 (7.21) | 9 (9.09) | 26 (6.33) |
| Muscle spasms | 0.212 | 1 (0.90) | 3 (3.33) | 4 (3.60) | 6 (6.06) | 14 (3.41) |
| Neck pain | 0.090 | 1 (0.90) | 1 (1.11) | 7 (6.31) | 3 (3.03) | 12 (2.92) |
| Pain in extremity | 0.628 | 3 (2.70) | 3 (3.33) | 2 (1.80) | 5 (5.05) | 13 (3.16) |

**Table 37. Treatment-Emergent Adverse Events Reported at a Frequency ≥5% - Number (%) of Subjects (Week 0 to Week 104)**

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Rheumatoid arthritis | <0.001*** | 12 (10.81) | 8 (8.89) | 5 (4.50) | 22 (22.22) | 47 (11.44) |
| Nervous system disorders | 0.759 | 33 (29.73) | 29 (32.22) | 36 (32.43) | 26 (26.26) | 124 (30.17) |
| Carpal tunnel syndrome | 0.252 | 1 (0.90) | 1 (1.11) | 2 (1.80) | 5 (5.05) | 9 (2.19) |
| Dizziness | 0.818 | 8 (7.21) | 6 (6.67) | 5 (4.50) | 5 (5.05) | 24 (5.84) |
| Headache | 0.807 | 14 (12.61) | 11 (12.22) | 18 (16.22) | 12 (12.12) | 55 (13.38) |
| Psychiatric disorders | 0.972 | 16 (14.41) | 13 (14.44) | 14 (12.61) | 13 (13.13) | 56 (13.63) |
| Depression | 0.168 | 3 (2.70) | 8 (8.89) | 7 (6.31) | 3 (3.03) | 21 (5.11) |
| Insomnia | 0.152 | 3 (2.70) | 0 | 2 (1.80) | 5 (5.05) | 10 (2.43) |
| Renal and urinary disorders | 0.694 | 14 (12.61) | 8 (8.89) | 9 (8.11) | 11 (11.11) | 42 (10.22) |
| Haematuria | 0.376 | 3 (2.70) | 7 (7.78) | 4 (3.60) | 4 (4.04) | 18 (4.38) |
| Respiratory, thoracic and mediastinal disorders | 0.945 | 32 (28.83) | 24 (26.67) | 28 (25.23) | 26 (26.26) | 110 (26.76) |
| Cough | 0.688 | 16 (14.41) | 13 (14.44) | 11 (9.91) | 14 (14.14) | 54 (13.14) |
| Pharyngolaryngeal pain | 0.576 | 5 (4.50) | 5 (5.56) | 6 (5.41) | 9 (9.09) | 25 (6.08) |
| Skin and subcutaneous tissue disorders | 0.602 | 39 (35.14) | 26 (28.89) | 30 (27.03) | 31 (31.31) | 126 (30.66) |
| Alopecia | 0.602 | 5 (4.50) | 2 (2.22) | 7 (6.31) | 4 (4.04) | 18 (4.38) |
| Eczema | 0.230 | 4 (3.60) | 1 (1.11) | 2 (1.80) | 6 (6.06) | 13 (3.16) |
| Erythema | 0.613 | 6 (5.41) | 3 (3.33) | 3 (2.70) | 2 (2.02) | 14 (3.41) |
| Pruritus | 0.361 | 4 (3.60) | 1 (1.11) | 6 (5.41) | 2 (2.02) | 13 (3.16) |
| Rash | 0.720 | 10 (9.01) | 8 (8.89) | 10 (9.01) | 13 (13.13) | 41 (9.98) |
| Vascular disorders | 0.572 | 16 (14.41) | 11 (12.22) | 19 (17.12) | 19 (19.19) | 65 (15.82) |
| Hypertension | 0.099 | 13 (11.71) | 6 (6.67) | 9 (8.11) | 17 (17.17) | 45 (10.95) |

Adverse events starting in Year 1 and continuing into Year 2 was tabulated in this report.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
E = etanercept; M = methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sub group.

a. Totals at a higher level are not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher level category.
b. Overall p-Value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and *** respectively.

Serious Adverse Events

The number and percentage of subjects who had serious adverse event (SAEs) during Week 52 to Week 104, by treatment group and overall, are shown in Table 38.

## Table 38. Number (%) of Subjects With Serious Adverse Events (Week 52 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Any Adverse Event | 0.536 | 8 (7.21) | 11 (12.22) | 10 (9.01) | 12 (12.12) | 41 (9.98) |
| Cardiac disorders | 0.026* | 0 | 3 (3.33) | 0 | 1 (1.01) | 4 (0.97) |
| Aortic valve stenosis | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Atrial fibrillation | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Atrioventricular block | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Mitral valve incompetence | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Myocardial infarction | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Gastrointestinal disorders | 0.797 | 0 | 1 (1.11) | 1 (0.90) | 1 (1.01) | 3 (0.73) |
| Abdominal pain upper | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Gastritis | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Gastrointestinal Haemorrhage | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Inguinal hernia | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| General disorders and administration site conditions | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| General physical health deterioration | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Systemic inflammatory response syndrome | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Infections and infestations | 0.949 | 1 (0.90) | 1 (1.11) | 2 (1.80) | 2 (2.02) | 6 (1.46) |
| Acute sinusitis | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Bursitis infective staphylococcal | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Pneumonia | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pneumonia streptococcal | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Tonsillitis | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Injury, poisoning and procedural complications | 0.463 | 4 (3.60) | 1 (1.11) | 4 (3.60) | 1 (1.01) | 10 (2.43) |
| Accidental overdose | 0.250 | 2 (1.80) | 0 | 0 | 0 | 2 (0.49) |
| Concussion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Device failure | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Fall | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Joint injury | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Ligament injury | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Overdose | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Procedural pain | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Skull fractured base | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Spinal compression fracture | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Musculoskeletal and connective tissue disorders | 0.507 | 2 (1.80) | 0 | 0 | 1 (1.01) | 3 (0.73) |
| Arthropathy | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Intervertebral disc protrusion | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Rheumatoid | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

## Table 38. Number (%) of Subjects With Serious Adverse Events (Week 52 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| arthritis | | | | | | |
| Spondylolisthesis acquired | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.023* | 0 | 5 (5.56) | 1 (0.90) | 3 (3.03) | 9 (2.19) |
| Basal cell carcinoma | 0.797 | 0 | 1 (1.11) | 1 (0.90) | 1 (1.01) | 3 (0.73) |
| Gastrointestinal carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Lung cancer metastatic | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Malignant melanoma of sites other than skin | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Metastases to lung | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Pancreatic carcinoma | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Prostate cancer | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Transitional cell carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Nervous system disorders | 0.459 | 0 | 2 (2.22) | 2 (1.80) | 1 (1.01) | 5 (1.22) |
| Cerebellar infarction | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Cerebral infarction | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Cerebrovascular accident | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Hydrocephalus | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Paraesthesia | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Sciatica | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| Psychiatric disorders | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Confusional state | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Renal and urinary disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Renal colic | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Reproductive system and breast disorders | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Testicular torsion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vaginal prolapse | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Respiratory, thoracic and mediastinal disorders | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Dyspnoea | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pulmonary embolism | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Surgical and medical procedures | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Cholecystectomy | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Haemorrhoid operation | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vascular disorders | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

## Table 38. Number (%) of Subjects With Serious Adverse Events (Week 52 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Aneurysm | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

Adverse events starting in year 1 and continuing into year 2 was tabulated in this report.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
E = etanercept; M = methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sub group.

a. Totals at a higher level are not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher level category.
b. Overall p-Value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by $^{*}$, $^{**}$, and $^{***}$ respectively.

The number and percentage of subjects who had SAEs during Week 0 to Week 104, by treatment group and overall are shown in Table 39.

**Table 39. Number (%) of Subjects With Serious Adverse Events (Week 0 to Week 104)**

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Any Adverse Event | 0.910 | 16 (14.41) | 13 (14.44) | 14 (12.61) | 16 (16.16) | 59 (14.36) |
| Cardiac disorders | 0.042* | 0 | 3 (3.33) | 0 | 2 (2.02) | 5 (1.22) |
| Aortic valve stenosis | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Atrial fibrillation | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Atrioventricular block | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Mitral valve incompetence | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Myocardial infarction | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Ventricular tachycardia | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Ear and labyrinth disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Vertigo | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Gastrointestinal disorders | 1.000 | 1 (0.90) | 1 (1.11) | 1 (0.90) | 1 (1.01) | 4 (0.97) |
| Abdominal pain upper | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Gastritis | 0.854 | 1 (0.90) | 0 | 0 | 1 (1.01) | 2 (0.49) |
| Gastrointestinal haemorrhage | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Inguinal hernia | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| General disorders and administration site conditions | 1.000 | 1 (0.90) | 1 (1.11) | 1 (0.90) | 1 (1.01) | 4 (0.97) |
| Chest pain | 0.854 | 1 (0.90) | 0 | 0 | 1 (1.01) | 2 (0.49) |
| General physical health deterioration | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Systemic inflammatory response syndrome | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Hepatobiliary disorders | 0.625 | 2 (1.80) | 0 | 1 (0.90) | 0 | 3 (0.73) |
| Cholelithiasis | 1.000 | 1 (0.90) | 0 | 1 (0.90) | 0 | 2 (0.49) |
| Gallbladder disorder | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Infections and infestations | 0.337 | 1 (0.90) | 3 (3.33) | 3 (2.70) | 5 (5.05) | 12 (2.92) |
| Acute sinusitis | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Bursitis infective staphylococcal | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Chronic sinusitis | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Diverticulitis | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Gastroenteritis | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Herpes zoster | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Any Adverse Event | 0.910 | 16 (14.41) | 13 (14.44) | 14 (12.61) | 16 (16.16) | 59 (14.36) |
| Lyme disease | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Pneumonia | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pneumonia streptococcal | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Skin infection | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Tonsillitis | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Injury, poisoning and procedural complications | 0.758 | 4 (3.60) | 2 (2.22) | 5 (4.50) | 2 (2.02) | 13 (3.16) |
| Accidental overdose | 0.402 | 2 (1.80) | 1 (1.11) | 0 | 0 | 3 (0.73) |
| Concussion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Device failure | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Fall | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |

## Table 39. Number (%) of Subjects With Serious Adverse Events (Week 0 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Joint injury | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Ligament injury | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Overdose | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Procedural pain | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Radius fracture | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Skull fractured base | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Spinal compression fracture | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Musculoskeletal and connective tissue disorders | 0.050* | 4 (3.60) | 0 | 0 | 3 (3.03) | 7 (1.70) |
| Arthropathy | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Intervertebral disc protrusion | 0.250 | 2 (1.80) | 0 | 0 | 0 | 2 (0.49) |
| Rheumatoid arthritis | 0.090 | 1 (0.90) | 0 | 0 | 3 (3.03) | 4 (0.97) |
| Spondylolisthesis acquired | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.234 | 1 (0.90) | 5 (5.56) | 2 (1.80) | 3 (3.03) | 11 (2.68) |
| Basal cell carcinoma | 0.797 | 0 | 1 (1.11) | 1 (0.90) | 1 (1.01) | 3 (0.73) |
| Bowen's disease | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Gastrointestinal carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Lung cancer metastatic | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Malignant melanoma of sites other than skin | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Metastases to lung | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Pancreatic carcinoma | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Prostate cancer | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| Transitional cell carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Nervous system disorders | 0.146 | 0 | 2 (2.22) | 4 (3.60) | 1 (1.01) | 7 (1.70) |
| Cerebellar infarction | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Cerebral infarction | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Cerebrovascular accident | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Hydrocephalus | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Paraesthesia | 0.250 | 0 | 0 | 2 (1.80) | 0 | 2 (0.49) |
| Sciatica | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| Syncope vasovagal | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Psychiatric disorders | 0.593 | 1 (0.90) | 1 (1.11) | 0 | 0 | 2 (0.49) |
| Confusional state | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Sleep disorder | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Renal and urinary disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Renal colic | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Reproductive system and breast disorders | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Testicular torsion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vaginal prolapse | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Respiratory, thoracic and mediastinal disorders | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Dyspnoea | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pulmonary embolism | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

## Table 39. Number (%) of Subjects With Serious Adverse Events (Week 0 to Week 104)

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Hyperhidrosis | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Surgical and medical procedures | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Cholecystectomy | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Haemorrhoid operation | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vascular disorders | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Aneurysm | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Any Adverse Event | 0.910 | 16 (14.41) | 13 (14.44) | 14 (12.61) | 16 (16.16) | 59 (14.36) |
| Lyme disease | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Pneumonia | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pneumonia streptococcal | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Skin infection | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Tonsillitis | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Injury, poisoning and procedural complications | 0.758 | 4 (3.60) | 2 (2.22) | 5 (4.50) | 2 (2.02) | 13 (3.16) |
| Accidental overdose | 0.402 | 2 (1.80) | 1 (1.11) | 0 | 0 | 3 (0.73) |
| Concussion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Device failure | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Fall | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Joint injury | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Ligament injury | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Overdose | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Procedural pain | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Radius fracture | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Skull fractured base | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Spinal compression fracture | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Musculoskeletal and connective tissue disorders | 0.050* | 4 (3.60) | 0 | 0 | 3 (3.03) | 7 (1.70) |
| Arthropathy | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Intervertebral disc protrusion | 0.250 | 2 (1.80) | 0 | 0 | 0 | 2 (0.49) |
| Rheumatoid arthritis | 0.090 | 1 (0.90) | 0 | 0 | 3 (3.03) | 4 (0.97) |
| Spondylolisthesis acquired | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0.234 | 1 (0.90) | 5 (5.56) | 2 (1.80) | 3 (3.03) | 11 (2.68) |
| Basal cell carcinoma | 0.797 | 0 | 1 (1.11) | 1 (0.90) | 1 (1.01) | 3 (0.73) |
| Bowen's disease | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Gastrointestinal carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Lung cancer metastatic | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Malignant melanoma of sites other than skin | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Metastases to lung | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Pancreatic carcinoma | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Prostate cancer | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| Transitional cell carcinoma | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |

**Table 39. Number (%) of Subjects With Serious Adverse Events (Week 0 to Week 104)**

| System Organ Class[a] Preferred Term | Overall p-Value[b] | Treatment E+M/E+M n=111 | M/M+E n=90 | E+M/E n=111 | M/M n=99 | Total n=411 |
|---|---|---|---|---|---|---|
| Nervous system disorders | 0.146 | 0 | 2 (2.22) | 4 (3.60) | 1 (1.01) | 7 (1.70) |
| Cerebellar infarction | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Cerebral infarction | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Cerebrovascular accident | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Hydrocephalus | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Paraesthesia | 0.250 | 0 | 0 | 2 (1.80) | 0 | 2 (0.49) |
| Sciatica | 0.593 | 0 | 1 (1.11) | 1 (0.90) | 0 | 2 (0.49) |
| Syncope vasovagal | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Psychiatric disorders | 0.593 | 1 (0.90) | 1 (1.11) | 0 | 0 | 2 (0.49) |
| Confusional state | 0.219 | 0 | 1 (1.11) | 0 | 0 | 1 (0.24) |
| Sleep disorder | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Renal and urinary disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Renal colic | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Reproductive system and breast disorders | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Testicular torsion | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vaginal prolapse | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Respiratory, thoracic and mediastinal disorders | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Dyspnoea | 0.356 | 0 | 1 (1.11) | 0 | 1 (1.01) | 2 (0.49) |
| Pulmonary embolism | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Skin and subcutaneous tissue disorders | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Hyperhidrosis | 1.000 | 1 (0.90) | 0 | 0 | 0 | 1 (0.24) |
| Surgical and medical procedures | 0.854 | 0 | 0 | 1 (0.90) | 1 (1.01) | 2 (0.49) |
| Cholecystectomy | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Haemorrhoid operation | 1.000 | 0 | 0 | 1 (0.90) | 0 | 1 (0.24) |
| Vascular disorders | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |
| Aneurysm | 0.460 | 0 | 0 | 0 | 1 (1.01) | 1 (0.24) |

Adverse events starting in Year 1 and continuing into Year 2 was tabulated in this report.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
E = etanercept; M = methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sub group.
a. Totals at a higher level are not necessarily the sum of those at the lower levels because a subject may report 2 or more different adverse events within the higher level category.
b. Overall p-Value: Fisher exact test p-value (2-tailed). Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by $^{*}$, $^{**}$, and $^{***}$ respectively.

Deaths:

During this 2-year interventional trial, there were 2 deaths: 1 in the ETN+MTX treatment group (Year 1) and 1 in the MTX/MTX treatment group (Year 2).

Malignancies:

Nine (9) malignancies occurred in 9 subjects during Week 52 to Week 104 of this study. The malignancies included 1 case each of digestive cancer (MTX/MTX+ETN), pancreas

carcinoma (MTX/MTX), basal cell carcinoma of the breast (ETN+MTX/ETN), basal cell carcinoma unspecified (MTX/MTX), cancer of chest wall and lungs (MTX/MTX), papillary transitional cell bladder carcinoma (MTX/MTX+ETN), rectal melanoma with metastasis to lung (MTX/MTX+ETN), a nodular cystic lesion diagnosed as basal cell cancer (MTX/MTX+ETN), and prostatic cancer (MTX/MTX+ETN). All but 1 of these subjects had a social history of being a smoker or a former smoker.

In addition to these malignancies, 1 case of prostatic adenocarcinoma (ETN+MTX/ETN) and Bowen disease (ETN+MTX/ETN+MTX) was reported during Week 0 to Week 104 of the study. These events were considered to be resolved in Year 1 and both subjects continued in Year 2 of the study.

Clinical Laboratory Evaluations

Laboratory test results that were Grade 3 or Grade 4 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) were considered to be of potential clinical importance (PCI) as presented in Table 40 and Table 41.

**Table 40. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance (Week 52 to Week 104), on Therapy Year 2**

| Category Test+Units[a] | Overall p-Value[b] | Treatment E+M/E+M | M/M+E | E+M/E | M/M | Total |
|---|---|---|---|---|---|---|
| Blood chemistry | | | | | | |
| Sodium | | | | | | |
| Grade 3 | 1.000 | 1/109 (0.9) | 0/87 | 0/107 | 0/93 | 1/396 (0.3) |
| Total bilirubin | | | | | | |
| Grade 3 | 0.063 | 3/109 (2.8) | 0/87 | 0/107 | 0/93 | 3/396 (0.8) |
| Grade 4 | 0.455 | 0/109 | 0/87 | 0/107 | 1/93 (1.1) | 1/396 (0.3) |
| Alkaline phosphatase | | | | | | |
| Grade 3 | 0.455 | 0/109 | 0/87 | 0/107 | 1/93 (1.1) | 1/396 (0.3) |
| Blood chemistry | | | | | | |
| Hematology | | | | | | |
| Hemoglobin | | | | | | |
| Grade 3 | 1.000 | 1/109 (0.9) | 0/87 | 0/106 | 0/93 | 1/395 (0.3) |
| White blood cells | | | | | | |
| Grade 3 | 0.220 | 0/109 | 1/87 (1.1) | 0/106 | 0/93 | 1/395 (0.3) |
| Neutrophils | | | | | | |
| Grade 3 | 0.220 | 0/109 | 1/87 (1.1) | 0/106 | 0/93 | 1/395 (0.3) |
| Lymphocytes | | | | | | |
| Grade 3 | 0.354 | 0/109 | 1/87 (1.1) | 0/106 | 1/93 (1.1) | 2/395 (0.5) |

E = etanercept; M = methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in sub group.
a. For each test, only the maximum grade per subjects was counted.
b. Fisher exact test p-value (2-tailed).

**Table 41. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance at the End of the Study (Termination Visit for Year 2)**

| Category Test+Units[a] | Overall p-Value[b] | Treatment E+M/E+M | M/M+E | E+M/E | M/M | Total |
|---|---|---|---|---|---|---|
| Blood chemistry | | | | | | |
| Total bilirubin | | | | | | |
| Grade 3 | 1.000 | 1/108 (0.9) | 0/86 | 0/108 | 0/94 | 1/396 (0.3) |
| Hematology | | | | | | |
| Hemoglobin | | | | | | |
| Grade 3 | 0.724 | 1/107 (0.9) | 0/85 | 0/108 | 0/92 | 1/392 (0.3) |
| Lymphocytes | | | | | | |
| Grade 3 | 0.217 | 0/107 | 1/85 (1.2) | 0/108 | 0/92 | 1/392 (0.3) |

E = etanercept; M = methotrexate.
a. For each test, only the maximum grade per subjects was counted.
b. Fisher exact test p-value (2-tailed).

The number and percentage of subjects with laboratory test results of PCI from the Year 1 Baseline, grouped by laboratory assessment, by treatment group and overall for Year 1 for

the on-therapy period, for Year 2 for the on-therapy period, and for the end of the study, are presented in Table 42 and Table 43.

**Table 42. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance (Week 0 to Week 104), on Therapy Year 1**

| Category Test+Units[a] | Overall p-Valu[b]e | Treatment E+M/E+M | M/M+E | E+M/E | M/M | Total |
|---|---|---|---|---|---|---|
| Blood chemistry | | | | | | |
| Potassium | | | | | | |
| Grade 4 | 1.000 | 1/111 (0.9) | 0/ 90 | 0/111 | 0/99 | 1/411 (0.2) |
| Total bilirubin | | | | | | |
| Grade 3 | 0.199 | 4/111 (3.6) | 0/ 90 | 1/111 (0.9) | 1/99 (1.0) | 6/411 (1.5) |
| SGPT/ALT | | | | | | |
| Grade 3 | 0.306 | 1/111 (0.9) | 0/ 90 | 0/111 | 2/99 (2.0) | 3/411 (0.7) |
| Hematology | | | | | | |
| Hemoglobin | | | | | | |
| Grade 3 | 0.854 | 1/111 (0.9) | 0/ 90 | 0/111 | 1/99 (1.0) | 2/411 (0.5) |
| Neutrophils | | | | | | |
| Grade 3 | 0.797 | 0/111 | 1/ 90 (1.1) | 1/111 (0.9) | 1/99 (1.0) | 3/411 (0.7) |
| Lymphocytes | | | | | | |
| Grade 3 | 0.065 | 0/111 | 3/ 90 (3.3) | 1/111 (0.9) | 4/99 (4.0) | 8/411 (1.9) |

ALT = alanine aminotransferase; E = etanercept; M = methotrexate.
a. For each test, only the maximum grade per subject was counted.
b. Fisher exact test p-value (2-tailed).

**Table 43. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance (Week 0 to Week 104), on Therapy Year 2**

| Category Test+Units[a] | Overall p-Value[b] | Treatment | | | | |
|---|---|---|---|---|---|---|
| | | E+M/E+M | M/M+E | E+M/E | M/M | Total |
| Blood chemistry | | | | | | |
| Sodium | | | | | | |
| Grade 3 | 1.000 | 1/109 (0.9) | 0/87 | 0/107 | 0/93 | 1/396 (0.3) |
| Total Bilirubin | | | | | | |
| Grade 3 | 0.063 | 3/109 (2.8) | 0/87 | 0/107 | 0/93 | 3/396 (0.8) |
| Grade 4 | 0.455 | 0/109 | 0/87 | 0/107 | 1/93 (1.1) | 1/396 (0.3) |
| Alkaline phosphatase | | | | | | |
| Grade 3 | 0.455 | 0/109 | 0/87 | 0/107 | 1/93 (1.1) | 1/396 (0.3) |
| Hematology | | | | | | |
| Hemoglobin | | | | | | |
| Grade 3 | 1.000 | 1/109 (0.9) | 0/ 87 | 0/106 | 0/93 | 1/395 (0.3) |
| White blood cells | | | | | | |
| Grade 3 | 0.220 | 0/109 | 1/87 (1.1) | 0/106 | 0/93 | 1/395 (0.3) |
| Neutrophils | | | | | | |
| Grade 3 | 0.220 | 0/109 | 1/87 (1.1) | 0/106 | 0/93 | 1/395 (0.3) |
| Lymphocytes | | | | | | |
| Grade 3 | 0.354 | 0/109 | 1/87 (1.1) | 0/106 | 1/93 (1.1) | 2/395 (0.5) |

E=etanercept; M=methotrexate.
a. For each test, only the maximum grade per subject was counted.
b. Fisher exact test p-value (2-tailed).

Number (%) of subjects with laboratory test results of potential clinical importance (Week 0 to Week 104), end of study is presented in Table 44.

**Table 44. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance (Week 0 to Week 104), End of Study**

| Category Test+Units[a] | Overall p-Value[b] | Treatment | | | | |
|---|---|---|---|---|---|---|
| | | E+M/E+M | M/M+E | E+M/E | M/M | Total |
| Blood Chemistry | | | | | | |
| Total Bilirubin | | | | | | |
| Grade 3 | 1.000 | 1/108 (0.9) | 0/86 | 0/108 | 0/94 | 1/396 (0.3) |
| Hematology | | | | | | |
| Hemoglobin | | | | | | |
| Grade 3 | 0.724 | 1/107 (0.9) | 0/85 | 0/108 | 0/92 | 1/392 (0.3) |
| Lymphocytes | | | | | | |
| Grade 3 | 0.217 | 0/107 | 1/85 (1.2) | 0/108 | 0/92 | 1/392 (0.3) |

E = etanercept; M = methotrexate.
a. For each test, only the maximum grade per subject was counted.
b. Fisher exact test p-value (2-tailed).

## CONCLUSIONS:

This was a 24-month, double-blind, randomized, 2-period, parallel-group, multicenter, outpatient study of the comparative efficacy of MTX treatment versus ETN+MTX treatment in subjects with active early RA (ie, disease duration of ≥3 months and ≤2 years). Period 1 and Period 2 of the study were each 12 months in duration.

A total of 411 subjects entered Year 2 of study. Of these, 361 subjects were eligible for the radiographic ITT population: 99 subjects in the ETN+MTX/ETN+MTX treatment group, 79 subjects in the MTX/MTX+ETN treatment group, 99 subjects in the ETN+MTX/ETN treatment group, and 84 subjects in the MTX/MTX treatment group.

The primary radiographic efficacy parameter was the change in modified TSS over 12 months, which was demonstrated to be significantly better with ETN+MTX/ETN+MTX treatment compared with MTX/ETN+MTX or MTX/MTX treatment.

The secondary radiographic endpoints were the change in modified TSS from Week 0 to Week 104 and the change in modified TSS from Week 52 to Week 104. The treatment comparisons for the change in modified TSS from Week 0 to Week 104 were similar to those observed during the first year; significantly greater improvement was shown for ETN+MTX/ETN+MTX treatment compared with MTX/ETN+MTX or MTX/MTX treatment. Between Week 52 and Week 104, significantly greater improvement in modified TSS was shown with ETN+MTX/ETN+MTX treatment compared with ETN+MTX/ETN treatment, but there was no significant difference between MTX/ETN+MTX and MTX/MTX treatment.

Additional radiographic endpoints included the proportion of subjects achieving no radiographic progression, the change in erosion and JSN scores, correlation between a response and radiographic nonprogression, and correlation of response with Baseline disease activity.

Significantly greater improvements were demonstrated between ETN+MTX/ETN+MTX and MTX/MTX treatment from Week 0 and Week 52 and Week 104 for erosion and JSN scores, with the exception of JSN score between Week 0 and Week 52. Between Weeks 52 and 104, treatment with ETN+MTX/ETN+MTX was significantly better than treatment with ETN+MTX/MTX in decreasing erosion, whereas there were no similar treatment differences observed for JSN scores.

Radiographic progression was significantly reduced with ETN+MTX/ETN+MTX treatment compared with MTX/MTX or MTX/ETN+MTX treatment when assessed as a change in modified TSS of ≤0.0, ≤0.5, ≤3.0, and at the SDD (2.756) from Week 0 to Week 52 and Week 52 to Week 104. The only exceptions were for analyses of radiographic progression ≤3.0 or at the SDD, which were not significantly different between ETN+MTX/ETN+MTX and MTX/ETN+MTX treatment from Week 52 to Week 104. From Week 52 to Week 104, ETN+MTX/ETN+MTX treatment was significantly better than ETN+MTX/ETN treatment for a change in modified TSS ≤0.0 and ≤0.5 and MTX/ETN+MTX was significantly better than MTX/MTX for a change modified TSS of ≤0.0 and at the SDD.

A weak correlation was observed for the change from Baseline in modified TSS of ≤0.0, ≤0.5, and ≤3.0 and DAS response. In addition, subjects with a Week 0 DAS score >5.1 had a significantly greater improvement in modified TSS with ETN+MTX/ETN+MTX treatment compared with MTX/ETN+MTX or MTX/MTX treatment from Week 0 to Weeks 52 and 104. This trend was also observed from Week 52 to Week 104 with greater improvement with ETN+MTX/ETN+MTX treatment compared with ETN+MTX/ETN treatment. There was no significant difference between MTX/ETN+MTX and MTX/MTX treatment.

During Year 2 of this study, combination therapy with ETN+MTX/ETN+MTX resulted in significantly greater slowing of radiographic progression compared with subjects who received MTX/MTX. This benefit was associated with significantly greater improvements in modified TSS, and erosion and JSN scores through 2 years of treatment. A weak correlation was observed for the change from Baseline in modified TSS of ≤0.0, ≤0.5, and ≤3.0 and DAS response. In addition, subjects treated with a DAS 28 score >5.1 at Week 0 who received ETN+MTX/ETN+MTX showed significantly greater improvement in modified TSS compared with subjects who received ETN+MTX/MTX, MTX/MTX, and ETN+MTX/ETN.

Continuous combination therapy with ETN+MTX/ETN+MTX also demonstrated a superior effect in modified TSS progression rate compared with the other MTX and ETN treatment combinations in this study. Maintaining ETN monotherapy after discontinuing MTX treatment after the first year of treatment was also effective in slowing the rate of modified TSS progression. The addition of ETN to MTX monotherapy considerably slowed radiographic progression; however, it was not as effective as continuous ETN+MTX combination therapy. Disease continued to progress with MTX monotherapy over 2 years.

Over 2 years in this interventional trial, ETN+MTX treatment was well tolerated. There were no new safety signals noted during the second year of the study. There were no differences among the treatment groups in the incidences of SAEs, serious infections, or trends in cardiovascular diseases. The differences in the occurrence of malignancies among

the groups showed no identifiable pattern. Additionally, there were no reported cases of tuberculosis, demyelinating disease, or lymphoma.