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

**PROTOCOL NO.**: 0881A1-4423 (B1801003)

**PROTOCOL TITLE**: A Randomized, Double-Blind Study Comparing the Safety and Efficacy of Once Weekly Administration of Etanercept 50 mg, Etanercept 25 mg, and Placebo in Combination With Methotrexate in Subjects With Moderately Active Rheumatoid Arthritis who Have Achieved an Adequate Response With Etanercept 50 mg Once Weekly and Methotrexate

**Study Centers:** A total of 79 centers took part in the study and randomized subjects; 8 centers France, 7 centers each in Australia and the Republic of Korea, 6 centers each in Mexico, Poland, Spain, and the Russian Federation, 5 center each in the Czech Republic, and Germany, 4 center each in Hungary, and Colombia, 3 centers each in Belgium, and Serbia and Montenegro, 2 centers each in Chile, and Italy, 1 center each in Netherlands, Sweden, Taiwan, Austria, and the United Kingdom.

**Study Initiation and Final Completion Dates**: 06 March 2008 to 30 May 2011

**Phase of Development**: Phase 4

**Study Objectives:**

Primary Objective: To compare the efficacy of the combination of etanercept 50 mg once weekly plus methotrexate (MTX) with that of MTX monotherapy at Week 88 in subjects with moderate rheumatoid arthritis (RA) who had achieved low disease activity or remission after 36-week treatment with open-label etanercept 50 mg once weekly plus MTX. The conditional primary objective was to compare the efficacy of the combination of etanercept 25 mg once weekly plus MTX with that of MTX monotherapy at Week 88 in subjects with moderate RA who had achieved low disease activity or remission after 36-week treatment with open-label etanercept 50 mg once weekly plus MTX.

The study hypothesis was that the combination of etanercept 50 mg once weekly plus MTX was superior to MTX monotherapy, as determined by the proportion of subjects remaining in low disease activity or remission at Week 88. The conditional hypothesis was that the combination of etanercept 25 mg once weekly plus MTX was superior to MTX monotherapy.

Secondary Objectives:

- To compare the efficacy of etanercept 50 mg once weekly plus MTX with etanercept 25 mg once weekly plus MTX at Week 88 in subjects with moderate RA who had

achieved low disease activity or remission after 36-week treatment with open-label etanercept 50 mg once weekly plus MTX.

- To assess the efficacy of etanercept 50 mg once weekly plus MTX over 36 weeks of the open-label period.

- To assess the safety of the treatment regimens over 36 weeks during the open-label period and 52 weeks of the double-blind period.

**METHODS**

**Study Design:** This was a multicenter, 2-period study that was conducted in subjects with RA who had moderate disease activity despite a stable dose of oral MTX (at least 15 mg/week and no more than 25 mg/week) for a minimum of 8 weeks at screening.

Period 1: An open-label, 36-week period in which all eligible subjects were treated with the combination of etanercept 50 mg once weekly plus MTX, at the same dose as the subject was receiving at the time of screening. A dose increase (up to 25 mg/week) for MTX was allowed at the discretion of the Investigator up to Week 28.

Period 2: A double-blind, randomized, 52-week period for subjects who were classified as sustained responders in Period 1. Responders were defined as subjects having a Disease Activity Score based on a 28-joint count (DAS28) ≤3.2 at the Week 36 visit. Only subjects with a DAS28 ≤3.2 at Week 36 and an average DAS28 ≤3.2 from the Week 12 visit through the Week 36 visit were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio and stratified based on low disease activity or remission using the individual Week 36 DAS28 value:

- Group A: etanercept 50 mg once weekly plus MTX (E50+M).

- Group B: etanercept 25 mg once weekly plus MTX (E25+M).

- Group C: etanercept placebo once weekly plus MTX (PBO+M).

The dose of MTX during the double-blind randomized period (Period 2) of the study was maintained at the same dose as the last 8 weeks of the open-label period (Period 1). Subjects who did not achieve the required response during the open-label period (Period 1) were withdrawn from the study before randomization.

The schedule of activities for the study is presented in Table 1.

## Table 1. Schedule of Activities

| **Study Week**[a] | **–35 to –4 Days** | **1** | **4** | **8** | **12** | **20** | **28** | **36**[b] | **40** | **48** | **56** | **64** | **72** | **80** | **88** | **90** | **Early Discontinuation Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Interval** | **Screening**[c] | **Baseline** | **Open-Label Period (Period 1)** | | | | | **Randomization (Period 2 Baseline)** | **Double-Blind Randomized Period (Period 2)** | | | | | | | **Follow-Up** | |
| **Visit ID (for sponsor use only)** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8**[d] | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16**[d] | **99**[d] |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | X | | | | | | | | | |
| Substance usage (alcohol and tobacco) | X | | | | | | | | | | | | | | X | | X |
| Washout of DMARD and NSAID therapy | | X | | | | | | | | | | | | | | | |
| Prior medications | X | X | | | | | | | | | | | | | | | |
| Concomitant medications | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Physical examination | X | X[e] | | | | | | X | | | | X | | | X | | X |
| Vital signs[f] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Joint assessment[g, h, i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Physician Global Assessment[g, i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Subject Global Assessment[i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Subject Morning Stiffness Assessment[i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| General health VAS[h, i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Pain VAS[i] | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Patient Acceptable Symptom State (PASS)[i] | | X | | | | | | X | | | | X | | | X | | X |
| HAQ[i, j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| EQ-5D[i, j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Medical Outcomes Study Sleep Scale[i, j] | | X | | | | | | X | | | | X | | | X | | X |
| FACIT Fatigue Scale[i, j] | | X | | | | | | X | | | | X | | | X | | X |
| Brief Pain Inventory (BPI)[i, j] | | X | | | | | | X | | | | X | | | X | | X |
| WPAI:RA Questionnaire[i, j] | | X | | | X | | | X | X | | X | | X | | X | | X |
| Pregnancy test[k] | X | X | | | | | | | | | | | | | | | |
| C-reactive protein | X | X[l] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Anticyclic citrullinated peptide | X | | | | | | | | | | | | | | | | |

## Table 1. Schedule of Activities

| Study Week[a] | –35 to –4 Days | 1 | 4 | 8 | 12 | 20 | 28 | 36[b] | 40 | 48 | 56 | 64 | 72 | 80 | 88 | 90 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Interval | Screening[c] | Baseline | Open-Label Period (Period 1) | | | | | Randomization (Period 2 Baseline) | Double-Blind Randomized Period (Period 2) | | | | | | | Follow-Up | Early Discontinuation Visit |
| Visit ID (for sponsor use only) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[d] | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16[d] | 99[d] |
| Erythrocyte sedimentation rate (ESR)[h, i, m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Rheumatoid factor | X | | | | | | | | | | | | | | | | |
| Chest radiograph / TB testing[n] | X | | | | | | | | | | | | | | | | |
| Hand, wrist, and forefoot radiographs | | X | | | | | | X | | | | | | | X | | X[o] |
| Urinalysis | X | X[l] | | | | | | X | | | | | | | X | | X |
| Blood chemistry and hematology | X | X[l] | | X | | X | | X | | X | X | X | X | X | X | | X |
| Fasting lipid profile[p] | | X | | | | | | X | | X | | | | | X | | X |
| Monitoring of adverse events[q] | X | ----------X | | | | | | | | | | | | | | | X |
| Randomization | | | | | | | | X | | | | | | | | | |
| Dispense investigational product | | X[r] | X | | X | X | X | X | X | X | X | X | X | X | | | |
| Return investigational product /drug accountability | | | X | | X | X | X | X | X | X | X | X | X | X | X | | X |
| Dispense subject investigational product diary | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Collect/review subject investigational product diary | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |

AE = adverse events; DAS28 = Disease Activity Score based on a 28-joint count; DMARD = disease-modifying antirheumatic drug; EQ-5D = EuroQol-5 Dimensions; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; ID = identification; NSAID = nonsteroidal anti-inflammatory drug; PPD = purified protein derivative; TB = tuberculosis; TNF = tumor necrosis factor; VAS = visual analog scale; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. The visit window for Weeks 4 through 88 was ±4 days. It was intended that all visit procedures would be completed on the same day (with the exception of fasting blood collection and radiographs).
b. The Week 36 visit was the end of Period 1 and the beginning of Period 2.
c. Screening visit procedures would have preferably all occurred on the same day. The Screening period was intended for the washout of prohibited medications and TB testing/prophylactic treatment as necessary per local standards. The Screening period was required to be a minimum of 4 days, but no more than 35 days, and may only have been extended to 42 days when TB prophylactic treatment was necessary. Results of all Screening procedures were required to be available at the Baseline visit to determine eligibility.
d. There was a follow-up telephone call to assess new and ongoing AEs: between 15 and 22 days after Week 36 if the subject was not randomly assigned to a group; between 15 and 22 days after early discontinuation, if the subject discontinued early from the study; or at Week 90: between 15 and 22 days after Week 88 if the subject completed the study.
e. The procedure did not need to be repeated at the Baseline visit if it was completed at the Screening visit ≤7 days before Baseline.

## Table 1. Schedule of Activities

| Study Week[a] | –35 to –4 Days | 1 | 4 | 8 | 12 | 20 | 28 | 36[b] | 40 | 48 | 56 | 64 | 72 | 80 | 88 | 90 | Early Discontinuation Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Interval | Screening[c] | Baseline | Open-Label Period (Period 1) | | | | | Randomization (Period 2 Baseline) | Double-Blind Randomized Period (Period 2) | | | | | | | Follow-Up | |
| Visit ID (for sponsor use only) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[d] | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16[d] | 99[d] |

f. Vital signs measurements included weight and height at screening, at Week 36 (randomization), at Week 88, or at the early discontinuation visit.
g. It was recommended that the same qualified personnel completed these assessments at each visit.
h. These procedures constituted the DAS28 examination and were done at all visits. However, only subjects with a DAS28 ≤3.2 at Week 36 and an average of ≤3.2 from the Week 12 visit through the Week 36 visit were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio and stratified based on low disease activity or remission using the individual Week 36 DAS28 value.
i. These procedures were recorded in an electronic hand-held diary.
j. Administered only to subjects in regions where valid translations were available.
k. For women of childbearing potential only. Serum test performed at Screening, urine test performed at the site at Baseline.
l. These laboratory tests did not need to be repeated at the Baseline visit if they were completed at the Screening visit ≤14 days before Baseline.
m. The ESR was performed at the investigative site using an ESR kit supplied by the centralized laboratory. ESR was to be completed at the subject's scheduled visit; however, to accommodate rare instances when the ESR blood sample was not drawn or the test was unable to be completed, the blood sample was drawn within +4 days of the scheduled visit to complete the DAS28 calculation for the visit.
n. Chest radiograph was performed at the Screening visit only and read locally by a qualified reader. Chest radiograph was not required if it had been done within the 12 months before Screening, the report was available, and was included in the subject's source documents. Local country guidelines were to be followed for appropriate TB screening and prophylaxis in the setting of anti-TNF therapy, including a minimum of a chest radiograph and objective TB testing (eg PPD, Quantiferon), depending on local guidelines. If the subject was known to be PPD or Quantiferon positive, the test was not repeated if documentation was available to show the subject met local guidelines for criteria for anti-TNF therapy and had not had TB in the last 2 years.
o. Hand, wrist, and forefoot radiographs were to be taken only if the subject discontinued from the study during the double-blind randomized period (Period 2).
p. Subjects were reminded to fast before the visit. All laboratory tests were collected at the subject's scheduled visit; however, to accommodate rare instances when a subject was unable to fast (or did not fast), all scheduled laboratory samples for the visit were drawn within +4 days of the visit.
q. From the signing of the informed consent form to Week 90.
r. The first dose was administered in the Investigator site office by study personnel after all Baseline evaluations were completed.

**Number of Subjects (Planned and Analyzed):** Approximately 900 subjects were planned in Period 1 with the expectation that approximately 60% of the subjects would have achieved low disease activity or remission at the end of Period 1. Thus, approximately 525 subjects were planned in Period 2 (175 subjects in each of the 3 treatment groups). A total of 834 subjects were enrolled in Period 1 and 756 subjects completed this period. A total of 604 subjects entered Period 2 and a total of 497 subjects completed this period.

**Diagnosis and Main Criteria for Inclusion:** Male and female subjects aged 18 to 70 years with moderate RA disease activity (as defined by a DAS28 >3.2 and ≤5.1) at both the Screening and Baseline visits, currently receiving an optimal dose of oral MTX (at least 15 mg/week but no more than 25 mg/week) for the treatment of RA were eligible for Period 1. Subjects who completed Period 1 and had a DAS28 ≤3.2 at Week 36 and an average of ≤3.2 from the Week 12 visit through the Week-36 visit were eligible for inclusion in Period 2.

Exclusion Criteria: Subjects with previous or current treatment with etanercept, other tumor necrosis factor-alpha (TNF) inhibitors, or other biologic agents or on concurrent treatment with any disease-modifying anti-rheumatoid drugs (DMARD) (other than MTX) within 28 days before Baseline or with more than 1 non-steroid anti-inflammatory drug (NSAID) at baseline were excluded from Period 1 of the study. Subjects that received a dose of an NSAID that changed within 14 days before the randomization visit (Week 36), received a dose of prednisone >10 mg/day (or equivalent) or had a dose changed within 14 days before the randomization visit (Week 36) or received an oral MTX dose that changed within 8 weeks before the Week 36 randomization visit (with the exception of a hold on the dose due to an AE) were excluded from Period 2.

**Study Treatment:**

Open-Label Period (Period 1): In Period 1, subjects received etanercept 50 mg once weekly subcutaneously (SC) with an oral dose of MTX (dosage range of MTX was 15 to 25 mg/week). The dose of etanercept was administered as a SC injection. The dose of MTX was the dose the subject was receiving at the time of screening. The dose of MTX may have been increased at the discretion of the Investigator during the open-label period (Period 1) through Week 28 to a maximum of 25 mg/week.

Double-Blind Randomized Period (Period 2): For Period 2 the Sponsor supplied double-blind individual subject packages containing 50 mg etanercept, 25 mg etanercept, or placebo for etanercept vials and syringes. The vials were blinded to look identical. MTX was supplied as open-label, repackaged commercial blisters of 2.5 mg tablets.

In Period 2, subjects were randomly assigned to 1 of 3 treatment groups:

- Group A: E50+M.
- Group B: E25+M.
- Group C: PBO+M.

The dose of MTX during Period 2 of the study was to be maintained at the same dose as the last 8 weeks of Period 1 and remain stable throughout Period 2 of the study. A dose increase of MTX was not allowed during Period 2. If the subject experienced an adverse event (AE) during Period 1 or 2, administration of MTX may have been withheld (≤2 doses) and/or the dose may have been decreased by 2.5 or 5.0 mg weekly (the minimum dose required to stay in the study was 10 mg/week) until tolerated. The goal was to achieve a stable dose of MTX; therefore, the subject may have remained at the new stable dose or may have retitrated back to the original dose. Retitration was allowed only once during the study and must have been approved by the medical monitor.

**Efficacy Endpoints:**

Primary Endpoint:

- Proportion of subjects with DAS28 ≤3.2 at Week 88 during Period 2.

Secondary Endpoints:

- Proportion of subjects achieving low disease activity or remission at each visit during Period 1 and Period 2.
- Change in the DAS28 during Period 1 and Period 2 at each visit.
- Time to loss of low disease activity (DAS28 >3.2) and a change of ≥0.6 in the DAS28 during Period 2.
- Time to loss of low disease activity (DAS28 >3.2) during Period 2.
- Proportion of time subjects have low disease activity.
- Change in the painful and swollen joint counts during Period 1 and Period 2 at each visit.
- Change in the physician global assessments during Period 1 and Period 2 at each visit.
- Change in the subject global assessments, including morning stiffness (measured in minutes), during Period 1 and Period 2 at each visit.
- Change in the general health visual analog scale (VAS), and pain VAS during Period 1 and Period 2 at each visit.
- Proportion of subjects achieving an acceptable state on the Patient Acceptable Symptom State (PASS) at various visits.
- Proportion of subjects achieving European League Against Rheumatism (EULAR) good or moderate responses during Period 1 and Period 2 at each visit.
- Proportion of subjects achieving American College of Rheumatology (ACR) 20, ACR 50, ACR 70, and ACR 90 during Period 1 and Period 2 at each visit.

**Safety Evaluations:** Safety was assessed by the reporting of physical examination, vital signs, hematology, blood chemistry profiles, lipid profiles, urinalysis, premature withdrawal, AEs, and serious AEs (SAEs) in all subjects who received at least 1 dose of study drug. All events that were due to the progression or fluctuation of RA or lack of response were not to be reported as an AE or SAE, because this type of information was captured in study assessments.

**Statistical Methods:** The modified intent to treat (MITT) population for Period 1 was the primary population and was same as the safety population, which was defined as all subjects who had taken at least 1 dose of open-label test article. The MITT population for Period 2 included all subjects who had taken at least 1 dose of double-blind investigational product, and had at least 1 post-randomization DAS28 evaluation. The mITT population was the primary population for period 2 efficacy analysis.

The per-protocol (PP) population was a subset of the mITT population, and excluded subjects who had major protocol deviation(s) that that could have potentially altered the interpretation of the efficacy analysis. The subjects who were to be excluded from the mITT population were identified prior to database release.

The Period 2 safety population included all randomized subjects who had taken at least 1 dose of double-blind investigational product. Safety analyses were based on the safety population.

For dichotomous endpoints, treatment groups were assessed in pairwise comparisons for proportion endpoints (which included the primary endpoint) from a Cochran-Mantel-Haenszel (CMH) statistic and adjusted odds ratio, stratified by Week 36 DAS28 strata (low disease activity or remission) at randomization and geographic region.

Changes from baseline endpoints were analyzed in analysis of covariance (ANCOVA) models with baseline as covariate and factors for treatment, geographic region, and DAS28 strata. In addition, descriptive statistics were determined for continuous endpoints, including n, mean, median, minimum, and maximum values. Ninety five percent confidence intervals (CIs) and p-values used a paired t-test (except for radiographic endpoints, which used a Wilcoxon signed rank test) to summarize within-group changes from both the Baseline visit (Week 1) and from the final value from randomization (Visit 8). Both ANCOVA analyses and descriptive statistics were obtained for each DAS28 strata subgroup separately.

Time-to-event analyses used the Kaplan Meier approach for estimation and the log rank test for statistical testing. There were 3 types of time-to-event analyses:

- For time-to-success events (eg time to DAS28 remission), the imputation of response approach censored subjects at final time point (Week 36 in Period 1, Week 88 in Period 2) for subjects who discontinued due to lack of efficacy (LOE), AE, protocol violation, or other reasons.

- For time-to-failure events (eg time-to-relapse) the imputation of failure approach imputed events at time of discontinuation for subjects who discontinued due to LOE, AE, protocol violation, or other reasons.

- For all time-to-event endpoints, the standard approach censored subjects who had not experienced the event at time of last observation.

Time-to-event analyses during Period 2 used the Kaplan-Meier approach for estimation and the log rank test for statistical testing. Time-to-event analyses were applied to discontinuations and loss of response in Period 2. For loss of response endpoints, discontinuation due to lack of efficacy was also treated as a loss response event.

Descriptive statistics were presented for the actual and change from Baseline values by treatment group for laboratory evaluations (hematology, blood chemistry, fasting lipid profile, and urinalysis), with overall treatment effect tested in an ANCOVA model, adjusted for Baseline of laboratory evaluation. Laboratory evaluations that had a significant treatment effect were then analyzed in pairwise comparisons of treatments to test for treatment differences. For each laboratory parameter, the proportion of subjects with at least 1 value of potential clinical importance was summarized by treatment group. The values of potential clinical importance are provided in the Clinical Data Presentation Plan document. Overall treatment effect was tested in a Fisher's exact test.

AEs were presented as the proportion of subjects with the AE. Overall treatment differences were tested by a chi-square test, with significant results then being further tested in pairwise comparisons using an exact Fisher's test.

**RESULTS**

**Subject Disposition and Demography:** Table 2 summarizes the primary reasons for withdrawal from Period 1 of the study. A total of 77 subjects discontinued from the study. Most subjects (90.6%) completed the study. The most common reason for discontinuation was unsatisfactory efficacy response, which led to discontinuation in 2.6% of the study population. The percentage of subjects who discontinued due to AEs was 2.2%.

**Table 2. Subject Disposition, Period 1**

| Conclusion Status Reason[a] | Treatment E50+M N=834 n (%) |
|---|---|
| Total | 833 (99.9) [b] |
| Completed | 756 (90.6) |
| Phase completed | 756 (90.6) |
| Discontinued | 77 (9.2) |
| Adverse event | 18 (2.2) |
| Death[c] | 1 (0.1) |
| Lost to follow-up | 1 (0.1) |
| Other | 21 (2.5) |
| Protocol violation | 14 (1.7) |
| Unsatisfactory response – efficacy | 22 (2.6) |

E50+M = etanercept 50 mg + methotrexate; N = Total number of subjects; n = number of subjects with observations.

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. There was a total of 834 subjects dosed; however, due to a data discrepancy at the time of the interim analysis 1 subject did not have a conclusion of subject participation record completed and therefore was not included in the total count.

c. A total of 2 subjects died in Period 1: one subject died on Study Day 31, and is accounted for in the conclusion status reason of 'Death'. One subject died on Study Day 79 and is instead accounted for in the conclusion status reason of 'Adverse Event'.

Of the 604 subjects who were eligible to enter Period 2, a total of 497 subjects (82.3%) completed this period (Table 3). Of the 107 subjects (17.7%) who did not complete Period 2, a smaller proportion were in the E50+M (21 subjects, 10.4%) and E25+M (27 subjects, 13.4%) treatment groups compared with the PBO+M group (59 subjects, 29.5%; $p<0.001$, in both cases).

**Table 3. Subject Disposition, Period 2**

| Disposition | Overall p-Value | Treatment E50+M n (%) | E25+M n (%) | PBO+M n (%) | Total n (%) |
|---|---|---|---|---|---|
| Total | | 202 (100) | 202 (100) | 200 (100) | 604 (100) |
| Phase completed | <0.001* | 181 (89.6) | 175 (86.6) | 141 (70.5) | 497 (82.3) |
| Discontinued[a] | <0.001*[b] | 21 (10.4) | 27 (13.4) | 59 (29.5) | 107 (17.7) |
| Adverse event | 0.641 | 7 (3.5) | 4 (2.0) | 5 (2.5) | 16 (2.6) |
| Death | 0.136 | 2 (1.0) | 0 | 0 | 2 (0.3) |
| Discontinuation of study by sponsor[c] | 0.136 | 0 | 2 (1.0) | 0 | 2 (0.3) |
| Lost to follow-up | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Other | 0.290 | 4 (2.0) | 5 (2.5) | 9 (4.5) | 18 (3.0) |
| Protocol violation | 0.674 | 4 (2.0) | 4 (2.0) | 2 (1.0) | 10 (1.7) |
| Unsatisfactory response - efficacy | <0.001*[b] | 4 (2.0) | 11 (5.4) | 43 (21.5) | 58 (9.6) |

* Statistical significance at the 0.001 level. Overall p-value (Chi-Square): refers to "Number of Subjects" data.

E25+M = etanercept 25 mg + methotrexate; E50+M = etanercept 50 mg + methotrexate; eCRF = electronic case report form; PBO+M = placebo + methotrexate; n = number of subjects.

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.
b. The E50+M versus PBO+M comparison was p<0.001; the E25+M versus PBO+M comparison was p<0.001.
c. These subjects were discontinued from the study due to protocol violations, but the Investigator reported the reason as 'discontinuation of study by Sponsor' on the eCRF. The study was not discontinued by the sponsor.

With the exception of duration of therapy, the 3 treatment groups were well-balanced with regard to their demographic and Baseline characteristics in Period 1 (Table 4). The mean (standard deviation [SD]) age of the study population overall was 47.61 (12.12) years, and ranged from 18 to 70 years. The majority of subjects were female (80.79%), and the study population was predominantly white (75.17%). Mean (SD) duration of RA was 6.84 (6.97) years.

## Table 4. Summary of Demographic and Baseline Characteristics (Period 1)

| Characteristic | p-Value | Treatment Group E50+M (n=202) | E25+M (n=202) | PBO+M (n=200) | Total (n=604) |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| N | | 202 | 202 | 200 | 604 |
| Mean (SD) | 0.244[a] | 48.12 (11.96) | 46.44 (12.18) | 48.27 (12.21) | 47.61 (12.12) |
| Min, Max | | 20.00, 69.00 | 18.00, 70.00 | 18.00, 69.00 | 18.00, 70.00 |
| Median | | 50.00 | 47.00 | 51.00 | 49.00 |
| Sex, n (%) | 0.334[b] | | | | |
| Female | | 164 (81.19) | 157 (77.72) | 167 (83.50) | 488 (80.79) |
| Male | | 38 (18.81) | 45 (22.28) | 33 (16.50) | 116 (19.21) |
| Race, n (%) | 0.659[b] | | | | |
| White | | 158 (78.22) | 145 (71.78) | 151 (75.50) | 454 (75.17) |
| Asian | | 21 (10.40) | 27 (13.37) | 22 (11.00) | 70 (11.59) |
| Black or African American | | 0 | 1 (0.50) | 0 | 1 (0.17) |
| Other | | 23 (11.39) | 29 (14.36) | 27 (13.50) | 79 (13.08) |
| Period 1 Baseline height (cm) | | | | | |
| N | | 202 | 202 | 200 | 604 |
| Mean (SD) | 0.336[a] | 163.90 (8.34) | 164.86 (8.80) | 163.69 (8.31) | 164.15 (8.49) |
| Min, Max | | 144.00, 195.00 | 143.00, 194.00 | 143.00, 196.00 | 143.00, 196.00 |
| Median | | 163.50 | 164.00 | 163.00 | 164.00 |
| Period 1 Baseline weight (kg) | | | | | |
| N | | 202 | 202 | 200 | 604 |
| Mean (SD) | 0.924[a] | 68.80 (12.96) | 69.31 (15.79) | 68.86 (13.29) | 68.99 (14.05) |
| Min, Max | | 44.00, 118.00 | 45.00, 122.00 | 46.00, 120.00 | 44.00, 122.00 |
| Median | | 68.00 | 65.00 | 65.50 | 66.00 |
| Period 1 Baseline BMI | | | | | |
| N | | 202 | 202 | 200 | 604 |
| Mean (SD) | 0.914[a] | 25.56 (4.18) | 25.44 (5.19) | 25.63 (4.25) | 25.54 (4.56) |
| Min, Max | | 16.90, 41.10 | 17.30, 44.20 | 16.70, 44.10 | 16.70, 44.20 |
| Median | | 24.95 | 24.20 | 25.15 | 24.80 |
| Primary diagnosis of RA, n (%) | | | | | |
| Yes | | 202 (100) | 202 (100) | 200 (100) | 604 (100) |
| Duration of disease (years) | | | | | |
| N | | 201 | 202 | 200 | 603 |
| Mean (SD) | 0.450[a] | 6.81 (7.17) | 6.42 (7.07) | 7.30 (6.67) | 6.84 (6.97) |
| Min, Max | | 0.15, 34.69 | 0.08, 45.07 | 0.25, 35.78 | 0.08, 45.07 |
| Median | | 3.89 | 3.68 | 5.13 | 4.33 |
| Missing | | 1 | 0 | 0 | 1 |
| Prior corticosteroid use, n (%) | 0.936[b] | | | | |
| Yes | | 122 (60.40) | 119 (58.91) | 121 (60.50) | 362 (59.93) |
| No | | 80 (39.60) | 83 (41.09) | 79 (39.50) | 242 (40.07) |
| Prior DMARD use,[c] n (%) | 0.848[b] | | | | |
| No | | 154 (76.24) | 149 (73.76) | 150 (75.00) | 453 (75.00) |
| Yes | | 48 (23.76) | 53 (26.24) | 50 (25.00) | 151 (25.00) |
| Prior NSAID use, n (%) | 0.619[b] | | | | |
| Yes | | 155 (76.73) | 147 (72.77) | 152 (76.00) | 454 (75.17) |
| No | | 47 (23.27) | 55 (27.23) | 48 (24.00) | 150 (24.83) |
| Prior methotrexate use, n (%) | | | | | |
| Yes | | 202 (100) | 202 (100) | 200 (100) | 604 (100) |

**Table 4. Summary of Demographic and Baseline Characteristics (Period 1)**

| Characteristic | p-Value | Treatment Group E50+M (n=202) | E25+M (n=202) | PBO+M (n=200) | Total (n=604) |
|---|---|---|---|---|---|
| Prior alcohol use, n (%) | 0.421[b] | | | | |
| No | | 179 (88.61) | 184 (91.09) | 174 (87.00) | 537 (88.91) |
| Yes | | 23 (11.39) | 18 (8.91) | 26 (13.00) | 67 (11.09) |
| Prior tobacco use, n (%) | 0.339[b] | | | | |
| No | | 160 (79.21) | 171 (84.65) | 161 (80.50) | 492 (81.46) |
| Yes | | 42 (20.79) | 31 (15.35) | 39 (19.50) | 112 (18.54) |

BMI = body mass index; DMARD = disease-modifying antirheumatic drug; E25+M = Etanercept 25 mg + Methotrexate; E50+M = Etanercept 50 mg + Methotrexate; max = maximum; min = minimum; MTX = methotrexate; N = total number of subjects; n = number of subjects with specified criteria; NSAID = nonsteroidal anti-inflammatory drug; PBO+M = Placebo + Methotrexate; RA = rheumatoid arthritis; SD = standard deviation.

a. One-way analysis of variance with treatment as factor.
b. p-Value for Chi-Square.
c. Excluding MTX.

**Efficacy Results:**

Primary Endpoint (Proportion of Subjects With DAS28 ≤3.2): E50+M treatment demonstrated statistically significant superiority over PBO+M treatment in the primary endpoint, the proportion of subjects with DAS28 low disease activity at Week 88 (LOE imputation). The proportion of subjects with DAS28 low disease activity in the E50+M treatment group was 82.6% compared with 42.6% in the PBO+M group (p<0.0001, Table 5). The adjusted odds ratio (95% CI) was 5.36 (3.2, 9.0).

E25+M treatment demonstrated statistically significant superiority over PBO+M treatment. The proportion of subjects with DAS28 low disease activity at Week 88 in the E25+M treatment group was 79.1% (p<0.0001, CMH test). The adjusted odds ratio (95% CI) was 4.81 (3.0, 7.6).

Change in DAS28: A descriptive summary for DAS28 change from Baseline in Period 1 among observed cases is presented in Table 6. By Week 36 the DAS28 score was reduced by 45.89% in the observed case analysis. Statistically significant differences in the change from Period 2 Baseline in adjusted mean DAS28 scores (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 7). The difference between the E50+M and E25+M treatment groups in change from Period 2 baseline at Week 88 was not statistically significant.

**Table 5. Proportion of Subjects With DAS28 Low Disease Activity at Week 88 (LOE Imputation), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 88 | 166/201 (82.6%) | 159/201 (79.1%) | 84/197 (42.6%) | E50+M | PBO+M | <0.0001 | 5.36 (3.2, 9.0) | 40.83 (32.5, 49.1) |
| | | | | E50+M | E25+M | 0.3805 | 1.15 (0.7, 2.0) | 6.65 (-0.5, 13.8) |
| | | | | E25+M | PBO+M | <0.0001 | 4.81 (3.0, 7.6) | 35.93 (27.0, 44.8) |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOE = lack of efficacy; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by geographic region. The p-value is from a CMH (Cochran-Mantel-Haenszel) test of general association, testing treatment effect on response, stratified by geographic region.

c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

**Table 6. Descriptive Summary for DAS28 During Period 1 in the mITT Population (Observed Cases)**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 829 | - | - | - |
| | Mean | 4.37 | - | - | - |
| | SD | 0.44 | - | - | - |
| | SE | 0.02 | - | - | - |
| | Median | 4.43 | - | - | - |
| | 95% lclm | 4.34 | - | - | - |
| | 95% uclm | 4.40 | - | - | - |
| | Min | 3.08 | - | - | - |
| | Max | 5.48 | - | - | - |
| | 25th percentile | 4.06 | - | - | - |
| | 75th percentile | 4.72 | - | - | - |
| Week 4 | N | 781 | 778 | 778 | <0.0001 |
| | Mean | 3.49 | -0.88 | -20.19 | - |
| | SD | 0.91 | 0.82 | 18.88 | - |
| | SE | 0.03 | 0.03 | 0.68 | - |
| | Median | 3.55 | -0.85 | -19.31 | - |
| | 95% lclm | 3.43 | -0.94 | -21.52 | - |
| | 95% uclm | 3.56 | -0.82 | -18.87 | - |
| | Min | 0.63 | -3.34 | -82.63 | - |
| | Max | 7.27 | 2.55 | 60.41 | - |
| | 25th percentile | 2.90 | -1.37 | -31.82 | - |
| | 75th percentile | 4.06 | -0.36 | -7.90 | - |
| Week 8 | N | 787 | 785 | 785 | <0.0001 |
| | Mean | 3.13 | -1.24 | -28.69 | - |
| | SD | 0.97 | 0.88 | 20.47 | - |
| | SE | 0.03 | 0.03 | 0.73 | - |
| | Median | 3.18 | -1.23 | -28.38 | - |
| | 95% lclm | 3.06 | -1.31 | -30.12 | - |
| | 95% uclm | 3.20 | -1.18 | -27.25 | - |
| | Min | 0.24 | -4.26 | -94.14 | - |
| | Max | 6.34 | 1.80 | 40.25 | - |
| | 25th percentile | 2.50 | -1.83 | -42.67 | - |
| | 75th percentile | 3.76 | -0.64 | -14.74 | - |
| Week 12 | N | 786 | 784 | 784 | <0.0001 |
| | Mean | 2.89 | -1.48 | -34.08 | - |
| | SD | 0.96 | 0.90 | 20.86 | - |
| | SE | 0.03 | 0.03 | 0.74 | - |
| | Median | 2.82 | -1.51 | -34.09 | - |
| | 95% lclm | 2.82 | -1.55 | -35.54 | - |
| | 95% uclm | 2.95 | -1.42 | -32.61 | - |
| | Min | 0.14 | -4.35 | -95.70 | - |
| | Max | 7.10 | 2.89 | 68.48 | - |
| | 25th percentile | 2.22 | -2.10 | -48.92 | - |
| | 75th percentile | 3.51 | -0.93 | -20.88 | - |
| Week 20 | N | 784 | 782 | 782 | <0.0001 |
| | Mean | 2.74 | -1.64 | -37.59 | - |
| | SD | 1.01 | 0.96 | 22.06 | - |
| | SE | 0.04 | 0.03 | 0.79 | - |
| | Median | 2.65 | -1.72 | -39.42 | - |

**Table 6. Descriptive Summary for DAS28 During Period 1 in the mITT Population (Observed Cases)**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | 95% lclm | 2.67 | -1.71 | -39.14 | - |
| | 95% uclm | 2.81 | -1.57 | -36.04 | - |
| | Min | 0.51 | -4.14 | -88.45 | - |
| | Max | 6.65 | 2.33 | 58.15 | - |
| | 25th percentile | 2.09 | -2.27 | -52.15 | - |
| | 75th percentile | 3.30 | -1.12 | -25.57 | - |
| Week 28 | N | 778 | 776 | 776 | <0.0001 |
| | Mean | 2.58 | -1.80 | -41.13 | - |
| | SD | 0.97 | 0.94 | 21.18 | - |
| | SE | 0.03 | 0.03 | 0.76 | - |
| | Median | 2.46 | -1.91 | -43.53 | - |
| | 95% lclm | 2.51 | -1.86 | -42.62 | - |
| | 95% uclm | 2.65 | -1.73 | -39.64 | - |
| | Min | 0.01 | -4.18 | -99.65 | - |
| | Max | 6.84 | 1.94 | 41.83 | - |
| | 25th percentile | 1.96 | -2.42 | -55.45 | - |
| | 75th percentile | 3.09 | -1.22 | -29.26 | - |
| Week 36 | N | 763 | 761 | 761 | <0.0001 |
| | Mean | 2.37 | -2.01 | -45.89 | - |
| | SD | 0.98 | 0.97 | 21.51 | - |
| | SE | 0.04 | 0.04 | 0.78 | - |
| | Median | 2.22 | -2.15 | -49.13 | - |
| | 95% lclm | 2.30 | -2.08 | -47.42 | - |
| | 95% uclm | 2.44 | -1.94 | -44.36 | - |
| | Min | 0.42 | -4.46 | -90.53 | - |
| | Max | 7.28 | 2.74 | 60.27 | - |
| | 25th percentile | 1.74 | -2.65 | -59.91 | - |
| | 75th percentile | 2.76 | -1.58 | -36.71 | - |

Percent Change from Baseline = 100*(observed value – Baseline value)/Baseline value.
DAS = disease activity score; lclm = lower confidence level limit; min = minimum; max = maximum; mITT = modified intent to treat; N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

**Table 7. Change From Period 2 Baseline in DAS28 (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 0.30 (0.06) | 197 | 0.31 (0.06) | 188 | 0.84 (0.06) | E50+M | PBO+M | <0.0001 | -0.54 (-0.7, -0.4) |
| | | | | | | | E50+M | E25+M | 0.9344 | -0.01 (-0.2, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.53 (-0.7, -0.4) |
| Week 48 | 201 | 0.40 (0.07) | 201 | 0.36 (0.07) | 197 | 1.25 (0.07) | E50+M | PBO+M | <0.0001 | -0.84 (-1.0, -0.7) |
| | | | | | | | E50+M | E25+M | 0.6173 | 0.05 (-0.1, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.89 (-1.1, -0.7) |
| Week 56 | 201 | 0.44 (0.07) | 201 | 0.37 (0.07) | 197 | 1.35 (0.07) | E50+M | PBO+M | <0.0001 | -0.92 (-1.1, -0.7) |
| | | | | | | | E50+M | E25+M | 0.5136 | 0.06 (-0.1, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.98 (-1.2, -0.8) |
| Week 64 | 201 | 0.47 (0.07) | 201 | 0.40 (0.07) | 197 | 1.33 (0.07) | E50+M | PBO+M | <0.0001 | -0.86 (-1.1, -0.7) |
| | | | | | | | E50+M | E25+M | 0.4868 | 0.07 (-0.1, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.93 (-1.1, -0.7) |
| Week 72 | 201 | 0.35 (0.08) | 201 | 0.38 (0.08) | 197 | 1.40 (0.08) | E50+M | PBO+M | <0.0001 | -1.05 (-1.3, -0.8) |
| | | | | | | | E50+M | E25+M | 0.7847 | -0.03 (-0.2, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.02 (-1.2, -0.8) |
| Week 80 | 201 | 0.40 (0.08) | 201 | 0.40 (0.08) | 197 | 1.42 (0.08) | E50+M | PBO+M | <0.0001 | -1.02 (-1.2, -0.8) |
| | | | | | | | E50+M | E25+M | 0.9810 | -0.00 (-0.2, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.02 (-1.2, -0.8) |
| Week 88 | 201 | 0.39 (0.08) | 201 | 0.50 (0.08) | 197 | 1.44 (0.08) | E50+M | PBO+M | <0.0001 | -1.04 (-1.3, -0.8) |
| | | | | | | | E50+M | E25+M | 0.3562 | -0.10 (-0.3, 0.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.94 (-1.2, -0.7) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region.

Proportion of Subjects With Low Disease Activity or Remission: At Week 36, 85.85% of subjects had DAS28 low disease activity, defined as ≤3.2 (Table 8), and 67.37% of subjects achieved DAS28 remission, defined as <2.6 (Table 9) in the observed case (OC) analysis.

**Table 8. Proportions of Subjects With DAS28 Low Disease During Period 1 in the mITT Population (Observed Cases)**

| Week | Treatment E50+M[a] n/N [%] (Exact 95% CI) | p-Value* |
|---|---|---|
| Baseline | 3/829 [0.36] (0.07, 1.05) | <0.0001 |
| Week 4 | 281/781 [35.98] (32.61, 39.46) | <0.0001 |
| Week 8 | 399/787 [50.70] (47.15, 54.25) | <0.0001 |
| Week 12 | 498/786 [63.36] (59.88, 66.74) | <0.0001 |
| Week 20 | 556/784 [70.92] (67.60, 74.08) | <0.0001 |
| Week 28 | 607/778 [78.02] (74.94, 80.88) | <0.0001 |
| Week 36 | 655/763 [85.85] (83.17, 88.24) | <0.0001 |

*Tests the null hypothesis that proportion is significantly different from zero using exact binomial test.
CI = confidence interval; DAS = disease activity score; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.
a. E50+M = Etanercept 50 mg + Methotrexate.

**Table 9. Proportions of Subjects Achieving DAS28 Remission During Period 1 in the mITT population (Observed Cases)**

| Week | Treatment E50+M[a] n/N [%] (Exact 95% CI) | p-Value* |
|---|---|---|
| Baseline | 0/ 829 ( 0.00, 0.44) | 0.9275 |
| Week 4 | 129/ 781 [16.52] (13.98, 19.31) | <0.0001 |
| Week 8 | 234/ 787 [29.73] (26.56, 33.06) | <0.0001 |
| Week 12 | 316/ 786 [40.20] (36.75, 43.73) | <0.0001 |
| Week 20 | 367/ 784 [46.81] (43.27, 50.37) | <0.0001 |
| Week 28 | 439/ 778 [56.43] (52.86, 59.95) | <0.0001 |
| Week 36 | 514/ 763 [67.37] (63.91, 70.69) | <0.0001 |

*Tests the null hypothesis that proportion is significantly different from zero using exact binomial test.
CI = confidence interval; DAS = disease activity score; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the proportions of subjects with DAS28 low disease activity were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 10). The difference between the E50+M group and E25+M group was not statistically significant.

Statistically significant differences in the proportions of subjects with DAS28 remission were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 11). The difference between the E50+M group and E25+M group was not statistically significant.

**Table 10. Proportion of Subjects with DAS28 Low Disease Activity (LOCF) in Period 2, mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 198/201 (98.5%) | 199/201 (99.0%) | 197/197 (100.0%) | E50+M | PBO+M | 0.0853 | 3.11 (0.5, 21.4) | -2.35 (-17.8, 13.1) |
| | | | | E50+M | E25+M | 0.8491 | 0.96 (0.2, 4.8) | -0.80 (-11.3, 9.7) |
| | | | | E25+M | PBO+M | 0.1278 | 3.97 (0.4, 42.5) | -1.66 (-18.6, 15.3) |
| Week 40 | 172/196 (87.8%) | 166/197 (84.3%) | 123/188 (65.4%) | E50+M | PBO+M | <0.0001 | 3.63 (2.1, 6.4) | 21.68 (13.5, 29.8) |
| | | | | E50+M | E25+M | 0.3027 | 1.43 (0.8, 2.7) | 4.63 (-2.2, 11.4) |
| | | | | E25+M | PBO+M | <0.0001 | 2.51 (1.5, 4.2) | 18.16 (9.5, 26.8) |
| Week 48 | 167/201 (83.1%) | 163/201 (81.1%) | 105/197 (53.3%) | E50+M | PBO+M | <0.0001 | 4.55 (2.7, 7.6) | 29.69 (21.2, 38.2) |
| | | | | E50+M | E25+M | 0.5871 | 1.18 (0.7, 2.1) | 3.82 (-3.6, 11.2) |
| | | | | E25+M | PBO+M | <0.0001 | 3.76 (2.3, 6.1) | 27.19 (18.2, 36.1) |
| Week 56 | 166/201 (82.6%) | 163/201 (81.1%) | 88/197 (44.7%) | E50+M | PBO+M | <0.0001 | 6.52 (3.9, 11.0) | 37.61 (29.1, 46.1) |
| | | | | E50+M | E25+M | 0.6716 | 1.14 (0.6, 2.0) | 3.08 (-4.4, 10.5) |
| | | | | E25+M | PBO+M | <0.0001 | 5.40 (3.4, 8.6) | 35.99 (27.2, 44.8) |
| Week 64 | 164/201 (81.6%) | 165/201 (82.1%) | 96/197 (48.7%) | E50+M | PBO+M | <0.0001 | 4.62 (2.8, 7.6) | 32.91 (24.2, 41.6) |
| | | | | E50+M | E25+M | 0.9399 | 0.88 (0.5, 1.5) | -0.11 (-7.9, 7.7) |
| | | | | E25+M | PBO+M | <0.0001 | 4.78 (3.0, 7.7) | 33.44 (24.7, 42.1) |
| Week 72 | 169/201 (84.1%) | 166/201 (82.6%) | 90/197 (45.7%) | E50+M | PBO+M | <0.0001 | 6.25 (3.7, 10.5) | 38.12 (29.5, 46.7) |
| | | | | E50+M | E25+M | 0.6692 | 1.08 (0.6, 1.9) | 1.95 (-5.3, 9.2) |
| | | | | E25+M | PBO+M | <0.0001 | 5.46 (3.4, 8.7) | 36.46 (27.7, 45.2) |
| Week 80 | 170/201 (84.6%) | 164/201 (81.6%) | 90/197 (45.7%) | E50+M | PBO+M | <0.0001 | 5.74 (3.4, 9.8) | 39.31 (30.9, 47.7) |
| | | | | E50+M | E25+M | 0.4326 | 1.20 (0.7, 2.1) | 4.44 (-2.7, 11.6) |
| | | | | E25+M | PBO+M | <0.0001 | 5.12 (3.2, 8.2) | 35.75 (27.0, 44.5) |
| Week 88 | 166/201 (82.6%) | 162/201 (80.6%) | 89/197 (45.2%) | E50+M | PBO+M | <0.0001 | 4.68 (2.8, 7.8) | 38.45 (30.1, 46.8) |
| | | | | E50+M | E25+M | 0.6064 | 1.03 (0.6, 1.8) | 5.47 (-1.8, 12.8) |
| | | | | E25+M | PBO+M | <0.0001 | 4.68 (3.0, 7.4) | 34.97 (26.1, 43.9) |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by geographic region.

c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

## Table 11. Proportion of Subjects With DAS28 Remission (LOCF) in Period 2, mITT Population

| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Treatment Compared: Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
|---|---|---|---|---|---|---|---|---|
| Week 36 | 163/201 (81.1%) | 160/201 (79.6%) | 158/197 (80.2%) | E50+M | PBO+M | 0.4626 | 1.30 (0.5, 3.3) | 1.79 (-6.0, 9.5) |
| | | | | E50+M | E25+M | 0.2886 | 1.44 (0.6, 3.3) | 1.55 (-5.9, 9.0) |
| | | | | E25+M | PBO+M | 0.7779 | 0.83 (0.4, 1.9) | 0.56 (-7.1, 8.2) |
| Week 40 | 135/196 (68.9%) | 125/197 (63.5%) | 80/188 (42.6%) | E50+M | PBO+M | <0.0001 | 2.94 (1.8, 4.7) | 25.85 (16.3, 35.4) |
| | | | | E50+M | E25+M | 0.2091 | 1.26 (0.8, 2.0) | 5.49 (-3.8, 14.8) |
| | | | | E25+M | PBO+M | <0.0001 | 2.31 (1.5, 3.6) | 20.71 (11.0, 30.4) |
| Week 48 | 132/201 (65.7%) | 126/201 (62.7%) | 72/197 (36.5%) | E50+M | PBO+M | <0.0001 | 3.33 (2.1, 5.2) | 29.16 (19.8, 38.5) |
| | | | | E50+M | E25+M | 0.5351 | 1.11 (0.7, 1.7) | 3.24 (-6.1, 12.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.12 (2.0, 4.8) | 26.33 (16.9, 35.7) |
| Week 56 | 125/201 (62.2%) | 131/201 (65.2%) | 57/197 (28.9%) | E50+M | PBO+M | <0.0001 | 4.09 (2.6, 6.5) | 32.51 (23.3, 41.7) |
| | | | | E50+M | E25+M | 0.4574 | 0.86 (0.5, 1.3) | -3.04 (-12.3, 6.2) |
| | | | | E25+M | PBO+M | <0.0001 | 5.04 (3.2, 8.0) | 36.46 (27.4, 45.5) |
| Week 64 | 128/201 (63.7%) | 123/201 (61.2%) | 60/197 (30.5%) | E50+M | PBO+M | <0.0001 | 4.19 (2.7, 6.6) | 33.05 (23.8, 42.3) |
| | | | | E50+M | E25+M | 0.5229 | 1.14 (0.7, 1.8) | 2.45 (-7.0, 11.9) |
| | | | | E25+M | PBO+M | <0.0001 | 3.84 (2.5, 6.0) | 30.93 (21.7, 40.2) |
| Week 72 | 135/201 (67.2%) | 131/201 (65.2%) | 55/197 (27.9%) | E50+M | PBO+M | <0.0001 | 5.36 (3.3, 8.6) | 39.02 (30.0, 48.0) |
| | | | | E50+M | E25+M | 0.6464 | 1.15 (0.7, 1.8) | 1.68 (-7.5, 10.9) |
| | | | | E25+M | PBO+M | <0.0001 | 4.79 (3.0, 7.6) | 37.59 (28.6, 46.6) |
| Week 80 | 135/201 (67.2%) | 130/201 (64.7%) | 59/197 (29.9%) | E50+M | PBO+M | <0.0001 | 4.96 (3.1, 7.9) | 37.03 (28.0, 46.1) |
| | | | | E50+M | E25+M | 0.5499 | 1.13 (0.7, 1.7) | 2.68 (-6.5, 11.9) |
| | | | | E25+M | PBO+M | <0.0001 | 4.11 (2.6, 6.4) | 34.87 (25.7, 44.1) |
| Week 88 | 134/201 (66.7%) | 121/201 (60.2%) | 58/197 (29.4%) | E50+M | PBO+M | <0.0001 | 4.41 (2.8, 7.0) | 37.08 (28.0, 46.2) |
| | | | | E50+M | E25+M | 0.1109 | 1.20 (0.8, 1.9) | 7.25 (-2.1, 16.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.85 (2.5, 6.0) | 31.08 (21.9, 40.3) |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

## Table 11. Proportion of Subjects With DAS28 Remission (LOCF) in Period 2, mITT Population

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by geographic region.
c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

Time in Low Disease Activity: The mean (SD) cumulative proportion of time spent with DAS28 low disease activity, from Week 36 to Week 88 (LOCF), was 0.85 (0.26), 0.84 (0.25), and 0.58 (0.33) for subjects in the E50+M, E25+M, and PBO+M treatment groups, respectively (Table 12).

**Table 12. Cumulative Proportion of Time With DAS28 Low Disease Activity, Week 36 to Week 88 (LOCF), mITT Population**

| Week 36 Through: | Statistic | E50+M[a] | E25+M[a] | PBO+M[a] |
|---|---|---|---|---|
| Week 40 | N | 196 | 197 | 188 |
| | Mean | 0.93 | 0.92 | 0.83 |
| | SD | 0.19 | 0.19 | 0.24 |
| | SE | 0.01 | 0.01 | 0.02 |
| | 95% lclm | 0.90 | 0.89 | 0.79 |
| | 95% uclm | 0.96 | 0.94 | 0.86 |
| | Minimum | 0.00 | 0.00 | 0.50 |
| | 25th percentile | 1.00 | 1.00 | 0.50 |
| | Median | 1.00 | 1.00 | 1.00 |
| | 75th percentile | 1.00 | 1.00 | 1.00 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 48 | N | 201 | 201 | 197 |
| | Mean | 0.88 | 0.86 | 0.69 |
| | SD | 0.25 | 0.27 | 0.34 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.85 | 0.82 | 0.64 |
| | 95% uclm | 0.92 | 0.90 | 0.74 |
| | Minimum | 0.00 | 0.00 | 0.17 |
| | 25th percentile | 1.00 | 0.83 | 0.50 |
| | Median | 1.00 | 1.00 | 0.67 |
| | 75th percentile | 1.00 | 1.00 | 1.00 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 56 | N | 201 | 201 | 197 |
| | Mean | 0.86 | 0.84 | 0.63 |
| | SD | 0.25 | 0.27 | 0.34 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.83 | 0.80 | 0.58 |
| | 95% uclm | 0.90 | 0.88 | 0.68 |
| | Minimum | 0.00 | 0.10 | 0.10 |
| | 25th percentile | 0.80 | 0.80 | 0.40 |
| | Median | 1.00 | 1.00 | 0.70 |
| | 75th percentile | 1.00 | 1.00 | 1.00 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 64 | N | 201 | 201 | 197 |
| | Mean | 0.85 | 0.84 | 0.61 |
| | SD | 0.26 | 0.26 | 0.33 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.81 | 0.80 | 0.56 |
| | 95% uclm | 0.89 | 0.88 | 0.65 |
| | Minimum | 0.00 | 0.07 | 0.07 |
| | 25th percentile | 0.71 | 0.71 | 0.29 |
| | Median | 1.00 | 1.00 | 0.67 |
| | 75th percentile | 1.00 | 1.00 | 1.00 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 72 | N | 201 | 201 | 197 |
| | Mean | 0.85 | 0.84 | 0.59 |
| | SD | 0.26 | 0.26 | 0.33 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.81 | 0.80 | 0.55 |
| | 95% uclm | 0.88 | 0.88 | 0.64 |

**Table 12. Cumulative Proportion of Time With DAS28 Low Disease Activity, Week 36 to Week 88 (LOCF), mITT Population**

| Week 36 Through: | Statistic | E50+M[a] | E25+M[a] | PBO+M[a] |
|---|---|---|---|---|
| | Minimum | 0.00 | 0.06 | 0.06 |
| | 25th percentile | 0.78 | 0.78 | 0.28 |
| | Median | 1.00 | 1.00 | 0.67 |
| | 75th percentile | 1.00 | 1.00 | 0.89 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 80 | N | 201 | 201 | 197 |
| | Mean | 0.85 | 0.84 | 0.58 |
| | SD | 0.26 | 0.26 | 0.33 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.81 | 0.81 | 0.54 |
| | 95% uclm | 0.88 | 0.88 | 0.63 |
| | Minimum | 0.00 | 0.05 | 0.05 |
| | 25th percentile | 0.82 | 0.73 | 0.32 |
| | Median | 1.00 | 1.00 | 0.59 |
| | 75th percentile | 1.00 | 1.00 | 0.89 |
| | Maximum | 1.00 | 1.00 | 1.00 |
| Week 88 | N | 201 | 201 | 197 |
| | Mean | 0.85 | 0.84 | 0.58 |
| | SD | 0.26 | 0.25 | 0.33 |
| | SE | 0.02 | 0.02 | 0.02 |
| | 95% lclm | 0.81 | 0.80 | 0.53 |
| | 95% uclm | 0.88 | 0.87 | 0.63 |
| | Minimum | 0.00 | 0.04 | 0.04 |
| | 25th percentile | 0.85 | 0.73 | 0.31 |
| | Median | 1.00 | 1.00 | 0.58 |
| | 75th percentile | 1.00 | 1.00 | 0.88 |
| | Maximum | 1.00 | 1.00 | 1.00 |

For each subject at each time point, the proportion is calculated as the time-averaged AUC (AUC / number of weeks at that time point), with AUC calculated from Week 36 to Week 88.
AUC = area under the curve; DAS28 = Disease Activity Score in 28 joints; lclm = lower confidence limit; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence limit.
a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

Time to Loss of DAS-28: A statistically significant difference in time to loss of DAS28 low disease activity in Period 2 (OC data) was observed in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 13). The difference between the E50+M group and E25+M group was not statistically significant.

**Table 13. Time to Loss of DAS28 Low Disease Activity (>3.2) in Period 2 (Observed Cases), mITT Population**

| Survival Statistics | E50+M[a] | E25+M[a] | PBO+M[a] | p-Value |
|---|---|---|---|---|
| Censored subjects n/N (%) | 120/201 (59.7) | 123/201 (61.2) | 44/197 (22.3) | - |
| Kaplan-Meier 25th percentile, days (95% CI) | 134.0 (82.0, 194.0) | 88.0 (81.0, 185.0) | 29.0 (28.0, 31.0) | - |
| Kaplan-Meier median, days (95% CI) | NE (365.0, NE) | NE (NE, NE) | 87.0 (82.0, 134.0) | - |
| Kaplan-Meier 75th percentile, days (95% CI) | NE (NE, NE) | NE (NE, NE) | 247.0 (164.0, 364.0) | - |
| Kaplan-Meier survival estimate through Week 88 (95% CI) | 52.7% (41.7%, 62.6%) | 59.4% (52.0%, 66.0%) | 18.1% (12.5%, 24.6%) | - |
| Log-rank test for E50+M vs. PBO+M | - | - | - | <0.0001 |
| Log-rank test for E25+M vs. PBO+M | - | - | - | <0.0001 |
| Log-rank test for E50+M vs. E25+M | - | - | - | 0.8199 |

Week-88 censored data was censored at 388 days.
CI = confidence interval; E = etanercept; mITT = modified intent to treat; M = methotrexate; N = total number of subjects; n = number of subjects with observations; NE = not estimable.
a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

Time to Loss of DAS-28 and a Change in DAS28 of ≥0.6: A statistically significant difference in time-to-loss of DAS28 low disease activity and a change in DAS28 of ≥0.6 in Period 2 (OC data) were observed in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 14). The difference between the E50+M group and E25+M group was not statistically significant.

**Table 14. Time-to-Loss of DAS28 Low Disease Activity (>3.2) and a Change in DAS28 of ≥0.6 in Period 2 (Observed Cases), mITT Population**

| Survival Statistics | E50+M[a] | E25+M[a] | PBO+M[a] | p-Value |
|---|---|---|---|---|
| Censored subjects n/N (%) | 125/201 (62.2) | 128/201 (63.7) | 44/197 (22.3) | - |
| Kaplan-Meier 25th percentile, days (95% CI) | 137.0 (83.0, 239.0) | 136.0 (84.0, 197.0) | 29.0 (28.0, 50.0) | - |
| Kaplan-Meier median, days (95% CI) | NE (366.0, NE) | NE (NE, NE) | 89.0 (82.0, 137.0) | - |
| Kaplan-Meier 75th percentile, days (95% CI) | NE (NE, NE) | NE (NE, NE) | 249.0 (190.0, 364.0) | - |
| Kaplan-Meier survival estimate through Week 88 (95% CI) | 55.2% (44.2%, 64.9%) | 61.9% (54.5%, 68.4%) | 18.0% (12.4%, 24.4%) | - |
| Log-rank test for E50+M vs. PBO+M | - | - | - | <0.0001 |
| Log-rank test for E25+M vs. PBO+M | - | - | - | <0.0001 |
| Log-rank test for E50+M vs. E25+M | - | - | - | 0.7632 |

Week-88 censored data was censored at 388 days.
CI = confidence interval; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations; NE = not estimable; vs = versus.
a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

ACR Response: During Period 1, the proportions of subjects achieving a 20% through 90% ACR improvement increased within each ACR category over the 36 weeks. At Week 36 ACR20, ACR50, ACR70, and ACR90 responses were observed in 76.5%, 63.3%, 29.6%, and 8.9% of subjects, respectively. ACR20, ACR50 and ACR70 are presented in Table 15.

**Table 15. Proportions of Subjects Achieving ACR20, ACR50 and ACR70 During Period 1 in the mITT Population (Observed Cases)**

| | Treatment E50+M[a] | |
|---|---|---|
| **Week** | **n/N [%] (Exact 95% CI)** | **p-Value*** |
| ACR20 Week 4 | 302/ 782 [38.62] (35.19, 42.13) | <0.0001 |
| Week 8 | 428/ 786 [54.45] (50.90, 57.98) | <0.0001 |
| Week 12 | 494/ 786 [62.85] (59.37, 66.24) | <0.0001 |
| Week 20 | 539/ 784 [68.75] (65.38, 71.98) | <0.0001 |
| Week 28 | 572/ 777 [73.62] (70.37, 76.69) | <0.0001 |
| Week 36 | 582/ 761 [76.48] (73.30, 79.45) | <0.0001 |
| ACR50 Week 4 | 88/ 782 [11.25] (9.12, 13.68) | <0.0001 |
| Week 8 | 186/ 786 [23.66] (20.73, 26.79) | <0.0001 |
| Week 12 | 259/ 786 [32.95] (29.67, 36.36) | <0.0001 |
| Week 20 | 340/ 784 [43.37] (39.87, 46.92) | <0.0001 |
| Week 28 | 418/ 777 [53.80] (50.22, 57.35) | <0.0001 |
| Week 36 | 482/ 761 [63.34] (59.80, 66.77) | <0.0001 |
| ACR70 Week 4 | 22/ 782 [2.81] (1.77, 4.23) | <0.0001 |
| Week 8 | 55/ 786 [7.00] (5.31, 9.01) | <0.0001 |
| Week 12 | 84/ 786 [10.69] (8.61, 13.06) | <0.0001 |
| Week 20 | 137/ 784 [17.47] (14.88, 20.32) | <0.0001 |
| Week 28 | 184/ 777 [23.68] (20.73, 26.83) | <0.0001 |
| Week 36 | 225/ 761 [29.57] (26.34, 32.95) | <0.0001 |

*Tests the null hypothesis that proportion is significantly different from zero using exact binomial test.
ACR = American College of Rheumatology; CI = confidence interval; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the proportions of subjects with an ACR 20 response were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 16). The difference between the E50+M group and E25+M group was not statistically significant.

Statistically significant differences in the proportions of subjects with an ACR 50 response were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 17). The difference between the E50+M group and E25+M group was not statistically significant.

Statistically significant differences in the proportions of subjects with an ACR 70 response were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 18). The difference between the E50+M group and E25+M group was not statistically significant.

Statistically significant differences in the proportions of subjects with an ACR 90 response were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups

when compared with the PBO+M group (Table 19). The difference between the E50+M group and E25+M group was not statistically significant.

**Table 16. Proportion of Subjects, in Period 2, With an ACR 20 Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 173/200 (86.5%) | 171/201 (85.1%) | 174/197 (88.3%) | E50+M | PBO+M | 0.6006 | 0.83 (0.4, 1.6) | -1.07 (-7.5, 5.4) |
| | | | | E50+M | E25+M | 0.4967 | 1.10 (0.6, 2.1) | -0.85 (-7.8, 6.1) |
| | | | | E25+M | PBO+M | 0.3648 | 0.76 (0.4, 1.5) | 0.20 (-6.3, 6.7) |
| Week 40 | 150/195 (76.9%) | 153/197 (77.7%) | 115/188 (61.2%) | E50+M | PBO+M | 0.0024 | 1.98 (1.2, 3.2) | 15.55 (6.7, 24.4) |
| | | | | E50+M | E25+M | 0.8308 | 0.92 (0.6, 1.5) | 0.67 (-7.6, 8.9) |
| | | | | E25+M | PBO+M | 0.0008 | 2.13 (1.3, 3.4) | 15.89 (6.8, 25.0) |
| Week 48 | 154/200 (77.0%) | 153/201 (76.1%) | 99/197 (50.3%) | E50+M | PBO+M | <0.0001 | 3.25 (2.0, 5.2) | 26.92 (18.0, 35.8) |
| | | | | E50+M | E25+M | 0.7374 | 1.09 (0.7, 1.8) | 1.63 (-6.3, 9.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.04 (1.9, 4.8) | 25.65 (16.7, 34.6) |
| Week 56 | 150/200 (75.0%) | 150/201 (74.6%) | 99/197 (50.3%) | E50+M | PBO+M | <0.0001 | 3.03 (1.9, 4.8) | 25.44 (16.5, 34.4) |
| | | | | E50+M | E25+M | 0.9599 | 1.05 (0.6, 1.7) | 1.65 (-6.6, 9.9) |
| | | | | E25+M | PBO+M | <0.0001 | 2.98 (1.9, 4.6) | 24.31 (15.2, 33.4) |
| Week 64 | 153/200 (76.5%) | 149/201 (74.1%) | 96/197 (48.7%) | E50+M | PBO+M | <0.0001 | 3.59 (2.3, 5.7) | 27.94 (18.9, 37.0) |
| | | | | E50+M | E25+M | 0.4509 | 1.23 (0.8, 2.0) | 2.06 (-6.4, 10.5) |
| | | | | E25+M | PBO+M | <0.0001 | 2.96 (1.9, 4.6) | 25.84 (16.9, 34.8) |
| Week 72 | 156/200 (78.0%) | 150/201 (74.6%) | 93/197 (47.2%) | E50+M | PBO+M | <0.0001 | 4.28 (2.6, 7.0) | 30.62 (21.7, 39.5) |
| | | | | E50+M | E25+M | 0.3037 | 1.20 (0.7, 2.0) | 3.99 (-4.2, 12.2) |
| | | | | E25+M | PBO+M | <0.0001 | 3.27 (2.1, 5.1) | 27.10 (18.0, 36.3) |
| Week 80 | 159/200 (79.5%) | 156/201 (77.6%) | 92/197 (46.7%) | E50+M | PBO+M | <0.0001 | 4.41 (2.7, 7.2) | 33.03 (24.2, 41.9) |
| | | | | E50+M | E25+M | 0.6076 | 1.13 (0.7, 1.9) | 2.65 (-5.2, 10.5) |
| | | | | E25+M | PBO+M | <0.0001 | 3.80 (2.4, 6.0) | 30.76 (21.9, 39.7) |
| Week 88 | 151/200 (75.5%) | 150/201 (74.6%) | 96/197 (48.7%) | E50+M | PBO+M | <0.0001 | 2.85 (1.8, 4.6) | 27.45 (18.4, 36.5) |
| | | | | E50+M | E25+M | 0.7837 | 0.95 (0.6, 1.6) | 2.29 (-6.2, 10.8) |
| | | | | E25+M | PBO+M | <0.0001 | 3.03 (2.0, 4.7) | 26.02 (17.0, 35.1) |

ACR = American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

**Table 16. Proportion of Subjects, in Period 2, With an ACR 20 Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.
c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

**Table 17. Proportion of Subjects, in Period 2, With an ACR 50 Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 153/200 (76.5%) | 142/201 (70.6%) | 146/197 (74.1%) | E50+M | PBO+M | 0.5263 | 1.20 (0.7, 2.0) | 2.60 (-5.8, 11.0) |
| | | | | E50+M | E25+M | 0.1055 | 1.41 (0.9, 2.3) | 5.14 (-3.1, 13.4) |
| | | | | E25+M | PBO+M | 0.4348 | 0.85 (0.5, 1.4) | -2.53 (-11.0, 5.9) |
| Week 40 | 118/195 (60.5%) | 114/197 (57.9%) | 77/188 (41.0%) | E50+M | PBO+M | 0.0003 | 2.16 (1.4, 3.3) | 19.25 (9.7, 28.9) |
| | | | | E50+M | E25+M | 0.5511 | 1.11 (0.7, 1.7) | 3.61 (-6.0, 13.2) |
| | | | | E25+M | PBO+M | 0.0013 | 1.92 (1.3, 2.9) | 16.51 (6.8, 26.3) |
| Week 48 | 116/200 (58.0%) | 119/201 (59.2%) | 66/197 (33.5%) | E50+M | PBO+M | <0.0001 | 2.79 (1.8, 4.3) | 24.59 (15.2, 34.0) |
| | | | | E50+M | E25+M | 0.9225 | 0.97 (0.6, 1.5) | -0.31 (-9.7, 9.1) |
| | | | | E25+M | PBO+M | <0.0001 | 2.95 (1.9, 4.5) | 24.75 (15.5, 34.0) |
| Week 56 | 124/200 (62.0%) | 113/201 (56.2%) | 57/197 (28.9%) | E50+M | PBO+M | <0.0001 | 4.20 (2.7, 6.6) | 32.79 (23.7, 41.8) |
| | | | | E50+M | E25+M | 0.2454 | 1.32 (0.9, 2.0) | 6.74 (-2.6, 16.1) |
| | | | | E25+M | PBO+M | <0.0001 | 3.15 (2.0, 4.9) | 26.95 (17.8, 36.1) |
| Week 64 | 118/200 (59.0%) | 112/201 (55.7%) | 55/197 (27.9%) | E50+M | PBO+M | <0.0001 | 3.83 (2.4, 6.0) | 30.62 (21.4, 39.8) |
| | | | | E50+M | E25+M | 0.4919 | 1.22 (0.8, 1.9) | 4.01 (-5.6, 13.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.16 (2.0, 4.9) | 27.43 (18.2, 36.6) |
| Week 72 | 126/200 (63.0%) | 108/201 (53.7%) | 53/197 (26.9%) | E50+M | PBO+M | <0.0001 | 4.80 (3.0, 7.6) | 35.79 (26.7, 44.9) |
| | | | | E50+M | E25+M | 0.0658 | 1.47 (1.0, 2.3) | 9.67 (0.2, 19.1) |
| | | | | E25+M | PBO+M | <0.0001 | 3.03 (2.0, 4.7) | 26.42 (17.2, 35.6) |
| Week 80 | 125/200 (62.5%) | 118/201 (58.7%) | 54/197 (27.4%) | E50+M | PBO+M | <0.0001 | 4.32 (2.7, 6.8) | 35.09 (26.0, 44.2) |
| | | | | E50+M | E25+M | 0.4014 | 1.25 (0.8, 1.9) | 4.55 (-4.9, 14.0) |
| | | | | E25+M | PBO+M | <0.0001 | 3.54 (2.3, 5.5) | 31.29 (22.2, 40.4) |
| Week 88 | 125/200 (62.5%) | 115/201 (57.2%) | 51/197 (25.9%) | E50+M | PBO+M | <0.0001 | 4.53 (2.9, 7.2) | 36.39 (27.4, 45.4) |
| | | | | E50+M | E25+M | 0.2824 | 1.23 (0.8, 1.9) | 6.21 (-3.3, 15.7) |
| | | | | E25+M | PBO+M | <0.0001 | 3.83 (2.5, 5.9) | 31.44 (22.4, 40.5) |

ACR = American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

**Table 17. Proportion of Subjects, in Period 2, With an ACR 50 Response From the Period 1 Baseline (LOCF), mITT Population**

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.
c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

**Table 18. Proportion of Subjects, in Period 2, With an ACR 70 Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 84/200 (42.0%) | 67/201 (33.3%) | 65/197 (33.0%) | E50+M | PBO+M | 0.0575 | 1.49 (1.0, 2.3) | 9.39 (0.0, 18.8) |
| | | | | E50+M | E25+M | 0.0630 | 1.48 (1.0, 2.3) | 9.83 (0.6, 19.1) |
| | | | | E25+M | PBO+M | 0.9160 | 1.02 (0.7, 1.6) | -0.30 (-9.3, 8.7) |
| Week 40 | 56/195 (28.7%) | 55/197 (27.9%) | 33/188 (17.6%) | E50+M | PBO+M | 0.0147 | 1.76 (1.0, 3.0) | 10.72 (2.3, 19.2) |
| | | | | E50+M | E25+M | 0.8675 | 1.02 (0.6, 1.6) | 0.76 (-8.0, 9.6) |
| | | | | E25+M | PBO+M | 0.0174 | 1.77 (1.1, 3.0) | 10.27 (1.9, 18.7) |
| Week 48 | 56/200 (28.0%) | 62/201 (30.8%) | 19/197 (9.6%) | E50+M | PBO+M | <0.0001 | 3.24 (1.9, 5.7) | 17.94 (10.3, 25.6) |
| | | | | E50+M | E25+M | 0.4941 | 0.85 (0.5, 1.3) | -1.61 (-10.4, 7.2) |
| | | | | E25+M | PBO+M | <0.0001 | 4.01 (2.3, 7.0) | 19.84 (12.0, 27.6) |
| Week 56 | 62/200 (31.0%) | 63/201 (31.3%) | 20/197 (10.2%) | E50+M | PBO+M | <0.0001 | 3.40 (2.0, 5.9) | 19.54 (11.6, 27.5) |
| | | | | E50+M | E25+M | 0.8185 | 0.95 (0.6, 1.5) | 0.56 (-8.5, 9.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.66 (2.1, 6.4) | 19.63 (11.7, 27.6) |
| Week 64 | 66/200 (33.0%) | 58/201 (28.9%) | 20/197 (10.2%) | E50+M | PBO+M | <0.0001 | 3.78 (2.2, 6.6) | 22.60 (14.7, 30.5) |
| | | | | E50+M | E25+M | 0.4254 | 1.17 (0.7, 1.8) | 5.39 (-3.6, 14.4) |
| | | | | E25+M | PBO+M | <0.0001 | 3.38 (1.9, 5.9) | 16.84 (9.1, 24.5) |
| Week 72 | 64/200 (32.0%) | 63/201 (31.3%) | 21/197 (10.7%) | E50+M | PBO+M | <0.0001 | 3.26 (1.8, 5.8) | 22.29 (14.4, 30.2) |
| | | | | E50+M | E25+M | 0.8766 | 1.06 (0.7, 1.6) | 0.76 (-8.4, 9.9) |
| | | | | E25+M | PBO+M | <0.0001 | 3.67 (2.1, 6.4) | 20.43 (12.9, 27.9) |
| Week 80 | 68/200 (34.0%) | 61/201 (30.3%) | 21/197 (10.7%) | E50+M | PBO+M | <0.0001 | 3.53 (2.0, 6.4) | 25.07 (17.5, 32.7) |
| | | | | E50+M | E25+M | 0.3535 | 1.21 (0.8, 1.9) | 4.03 (-5.1, 13.2) |
| | | | | E25+M | PBO+M | <0.0001 | 3.44 (1.9, 6.1) | 19.40 (12.0, 26.8) |
| Week 88 | 71/200 (35.5%) | 63/201 (31.3%) | 22/197 (11.2%) | E50+M | PBO+M | <0.0001 | 3.45 (2.0, 6.1) | 24.88 (16.7, 33.0) |
| | | | | E50+M | E25+M | 0.3231 | 1.25 (0.8, 1.9) | 4.17 (-4.9, 13.3) |
| | | | | E25+M | PBO+M | <0.0001 | 3.23 (1.9, 5.6) | 20.10 (12.5, 27.7) |

ACR = American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.

c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

**Table 19. Proportion of Subjects, in Period 2, With an ACR 90 Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 27/200 (13.5%) | 29/201 (14.4%) | 11/197 (5.6%) | E50+M | PBO+M | 0.0089 | 2.14 (0.9, 5.2) | 8.09 (-1.3, 17.5) |
| | | | | E50+M | E25+M | 0.6932 | 0.87 (0.5, 1.7) | 0.28 (-4.9, 5.5) |
| | | | | E25+M | PBO+M | 0.0019 | 2.76 (1.2, 6.1) | 7.89 (-1.6, 17.4) |
| Week 40 | 20/195 (10.3%) | 18/197 (9.1%) | 9/188 (4.8%) | E50+M | PBO+M | 0.0797 | 1.53 (0.6, 3.6) | 5.52 (-1.7, 12.7) |
| | | | | E50+M | E25+M | 0.8103 | 0.90 (0.4, 1.9) | 2.30 (-3.3, 7.9) |
| | | | | E25+M | PBO+M | 0.0903 | 1.87 (0.8, 4.5) | 4.35 (-4.3, 13.0) |
| Week 48 | 20/200 (10.0%) | 19/201 (9.5%) | 5/197 (2.5%) | E50+M | PBO+M | 0.0035 | 3.02 (1.2, 7.8) | 6.96 (-0.9, 14.8) |
| | | | | E50+M | E25+M | 0.9770 | 1.01 (0.5, 2.0) | 0.40 (-4.4, 5.2) |
| | | | | E25+M | PBO+M | 0.0036 | 3.29 (1.3, 8.3) | 6.54 (-1.0, 14.1) |
| Week 56 | 19/200 (9.5%) | 18/201 (9.0%) | 4/197 (2.0%) | E50+M | PBO+M | 0.0038 | 2.80 (1.0, 7.7) | 6.95 (-0.1, 14.0) |
| | | | | E50+M | E25+M | 0.9055 | 0.98 (0.5, 2.0) | 3.73 (-3.5, 11.0) |
| | | | | E25+M | PBO+M | 0.0020 | 3.36 (1.2, 9.8) | 6.77 (-0.1, 13.7) |
| Week 64 | 21/200 (10.5%) | 24/201 (11.9%) | 5/197 (2.5%) | E50+M | PBO+M | 0.0020 | 3.35 (1.3, 8.8) | 8.40 (0.2, 16.6) |
| | | | | E50+M | E25+M | 0.5763 | 0.87 (0.4, 1.7) | 2.86 (-4.9, 10.6) |
| | | | | E25+M | PBO+M | 0.0002 | 3.93 (1.5, 10.0) | 7.66 (-0.8, 16.1) |
| Week 72 | 24/200 (12.0%) | 28/201 (13.9%) | 5/197 (2.5%) | E50+M | PBO+M | 0.0004 | 3.21 (1.2, 8.8) | 10.47 (3.0, 17.9) |
| | | | | E50+M | E25+M | 0.4828 | 0.83 (0.4, 1.6) | 2.85 (-4.9, 10.6) |
| | | | | E25+M | PBO+M | <0.0001 | 3.52 (1.4, 9.0) | 10.76 (2.0, 19.5) |
| Week 80 | 28/200 (14.0%) | 26/201 (12.9%) | 6/197 (3.0%) | E50+M | PBO+M | 0.0002 | 3.28 (1.4, 7.8) | 10.71 (2.6, 18.8) |
| | | | | E50+M | E25+M | 0.8553 | 1.03 (0.6, 1.9) | 4.37 (-3.4, 12.2) |
| | | | | E25+M | PBO+M | 0.0003 | 3.56 (1.5, 8.7) | 8.09 (-0.3, 16.5) |
| Week 88 | 34/200 (17.0%) | 29/201 (14.4%) | 7/197 (3.6%) | E50+M | PBO+M | <0.0001 | 3.53 (1.6, 7.6) | 13.73 (5.3, 22.2) |
| | | | | E50+M | E25+M | 0.5025 | 1.12 (0.6, 2.0) | 6.75 (-1.6, 15.1) |
| | | | | E25+M | PBO+M | 0.0001 | 3.62 (1.6, 8.1) | 8.87 (0.2, 17.5) |

ACR = American College of Rheumatology; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

**Table 19. Proportion of Subjects, in Period 2, With an ACR 90 Response From the Period 1 Baseline (LOCF), mITT Population**

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value was from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.
c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

EULAR Response: Good EULAR response was defined as a DAS28 improvement from baseline of >1.2 units and a DAS28 endpoint result of ≤3.2 units. Good/moderate response was achieved by 90.80% of subjects at Week 36 in the observed case analysis (Table 20).

**Table 20 Proportions of Subjects With DAS28 Good/Moderate EULAR Response During Period 1 in the mITT Population (Observed Cases)**

| Week | Treatment E50+M[a] n/N [%] (Exact 95% CI) | p-Value* |
|---|---|---|
| Week 4 | 482/ 778 [ 61.95] ( 58.44, 65.38) | <0.0001 |
| Week 8 | 601/ 785 [ 76.56] ( 73.44, 79.48) | <0.0001 |
| Week 12 | 652/ 784 [ 83.16] ( 80.36, 85.72) | <0.0001 |
| Week 20 | 688/ 782 [ 87.98] ( 85.49, 90.18) | <0.0001 |
| Week 28 | 693/ 776 [ 89.30] ( 86.91, 91.39) | <0.0001 |
| Week 36 | 691/ 761 [ 90.80] ( 88.52, 92.76) | <0.0001 |

*Tests the null hypothesis that proportion is significantly different from zero using exact binomial test.
CI = confidence interval; DAS = disease activity score; EULAR = European League Against Rheumatism; mITT = modified intent to treat; n = number of subjects with DAS28 good EULAR response; N = number of subjects assessed at each time point.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the proportions of subjects with a EULAR good or moderate response were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group (Table 21). The difference between the E50+M group and E25+M group was not statistically significant.

**Table 21. Proportion of Subjects, in Period 2, With a EULAR Good or Moderate Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 198/200 (99.0%) | 199/201 (99.0%) | 192/197 (97.5%) | E50+M | PBO+M | 0.1718 | 2.29 (0.5, 10.7) | 1.75 (-6.9, 10.4) |
| | | | | E50+M | E25+M | 0.8303 | 1.17 (0.2, 7.3) | 0.12 (-11.1, 11.3) |
| | | | | E25+M | PBO+M | 0.2130 | 2.27 (0.5, 10.1) | 1.77 (-6.8, 10.4) |
| Week 40 | 183/195 (93.8%) | 188/197 (95.4%) | 143/188 (76.1%) | E50+M | PBO+M | <0.0001 | 4.10 (2.1, 8.2) | 16.77 (8.6, 25.0) |
| | | | | E50+M | E25+M | 0.4337 | 0.81 (0.3, 2.0) | -0.15 (-5.4, 5.1) |
| | | | | E25+M | PBO+M | <0.0001 | 5.14 (2.5, 10.8) | 18.61 (10.4, 26.8) |
| Week 48 | 182/200 (91.0%) | 185/201 (92.0%) | 126/197 (64.0%) | E50+M | PBO+M | <0.0001 | 5.61 (3.0, 10.5) | 26.97 (19.3, 34.6) |
| | | | | E50+M | E25+M | 0.8973 | 0.88 (0.4, 1.9) | -3.99 (-12.9, 4.9) |
| | | | | E25+M | PBO+M | <0.0001 | 5.33 (2.8, 10.1) | 26.69 (16.4, 36.9) |
| Week 56 | 180/200 (90.0%) | 184/201 (91.5%) | 127/197 (64.5%) | E50+M | PBO+M | <0.0001 | 4.40 (2.4, 8.1) | 25.28 (17.6, 33.0) |
| | | | | E50+M | E25+M | 0.5708 | 0.81 (0.4, 1.7) | -1.20 (-6.3, 3.9) |
| | | | | E25+M | PBO+M | <0.0001 | 5.58 (3.0, 10.3) | 26.39 (18.8, 34.0) |
| Week 64 | 184/200 (92.0%) | 184/201 (91.5%) | 123/197 (62.4%) | E50+M | PBO+M | <0.0001 | 6.29 (3.3, 12.0) | 29.24 (21.4, 37.0) |
| | | | | E50+M | E25+M | 0.8842 | 0.91 (0.4, 2.0) | -0.11 (-5.9, 5.7) |
| | | | | E25+M | PBO+M | <0.0001 | 5.92 (3.2, 10.8) | 28.67 (20.9, 36.5) |
| Week 72 | 186/200 (93.0%) | 179/201 (89.1%) | 121/197 (61.4%) | E50+M | PBO+M | <0.0001 | 7.39 (3.8, 14.4) | 31.97 (23.9, 40.1) |
| | | | | E50+M | E25+M | 0.1608 | 1.42 (0.6, 3.1) | 6.11 (0.1, 12.2) |
| | | | | E25+M | PBO+M | <0.0001 | 4.92 (2.9, 8.4) | 27.11 (19.1, 35.1) |
| Week 80 | 184/200 (92.0%) | 179/201 (89.1%) | 119/197 (60.4%) | E50+M | PBO+M | <0.0001 | 6.44 (3.4, 12.4) | 32.63 (24.5, 40.8) |
| | | | | E50+M | E25+M | 0.2825 | 1.21 (0.6, 2.7) | 4.90 (-1.0, 10.8) |
| | | | | E25+M | PBO+M | <0.0001 | 4.59 (2.7, 7.8) | 28.61 (20.6, 36.6) |
| Week 88 | 181/200 (90.5%) | 177/201 (88.1%) | 122/197 (61.9%) | E50+M | PBO+M | <0.0001 | 4.81 (2.7, 8.7) | 28.34 (18.7, 38.0) |
| | | | | E50+M | E25+M | 0.4471 | 1.06 (0.5, 2.1) | 7.03 (-1.6, 15.7) |
| | | | | E25+M | PBO+M | <0.0001 | 4.19 (2.5, 7.0) | 25.14 (16.9, 33.4) |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; EULAR = European League Against Rheumatism; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; n = number of subjects with observations.

**Table 21. Proportion of Subjects, in Period 2, With a EULAR Good or Moderate Response From the Period 1 Baseline (LOCF), mITT Population**

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.
c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

Morning Stiffness: The mean percent reduction in morning stiffness by Week 36 in the observed case analysis was 37.74% (Table 22).

**Table 22: Descriptive Summary for Morning Stiffness During Period 1 in the mITT Population (Observed Cases) Minute 00**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 830 | - | - | - |
| | Mean | 176.98 | - | - | - |
| | SD | 333.51 | - | - | - |
| | SE | 11.58 | - | - | - |
| | Median | 60.00 | - | - | - |
| | 95% lclm | 154.25 | - | - | - |
| | 95% uclm | 199.70 | - | - | - |
| | Min | 0.00 | - | - | - |
| | Max | 1440.00 | - | - | - |
| | 25th percentile | 30.00 | - | - | - |
| | 75th percentile | 150.00 | - | - | - |
| Week 4 | N | 776 | 773 | 710 | <0.0001 |
| | Mean | 93.72 | -81.31 | 7.63 | - |
| | SD | 218.94 | 335.75 | 389.57 | - |
| | SE | 7.86 | 12.08 | 14.62 | - |
| | Median | 30.00 | -15.00 | -40.00 | - |
| | 95% lclm | 78.29 | -105.02 | -21.08 | - |
| | 95% uclm | 109.15 | -57.61 | 36.33 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1410.00 | 5900.00 | - |
| | 25th percentile | 10.00 | -60.00 | -81.25 | - |
| | 75th percentile | 90.00 | 0.00 | 0.00 | - |
| Week 8 | N | 783 | 781 | 716 | <0.0001 |
| | Mean | 94.84 | -84.96 | 0.94 | - |
| | SD | 247.95 | 339.94 | 319.33 | - |
| | SE | 8.86 | 12.16 | 11.93 | - |
| | Median | 30.00 | -30.00 | -50.41 | - |
| | 95% lclm | 77.45 | -108.84 | -22.49 | - |
| | 95% uclm | 112.24 | -61.08 | 24.37 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1410.00 | 4700.00 | - |
| | 25th percentile | 5.00 | -84.00 | -90.63 | - |
| | 75th percentile | 90.00 | 0.00 | 0.00 | - |
| Week 12 | N | 773 | 771 | 709 | <0.0001 |
| | Mean | 78.97 | -93.86 | 12.50 | - |
| | SD | 232.06 | 367.21 | 494.82 | - |
| | SE | 8.35 | 13.22 | 18.58 | - |
| | Median | 20.00 | -30.00 | -66.67 | - |
| | 95% lclm | 62.59 | -119.82 | -23.99 | - |
| | 95% uclm | 95.36 | -67.90 | 48.98 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1420.00 | 7100.00 | - |
| | 25th percentile | 0.00 | -90.00 | -97.82 | - |
| | 75th percentile | 60.00 | 0.00 | -33.33 | - |
| Week 20 | N | 775 | 772 | 709 | <0.0001 |

**Table 22: Descriptive Summary for Morning Stiffness During Period 1 in the mITT Population (Observed Cases) Minute 00**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | Mean | 64.27 | -109.46 | 77.03 | - |
| | SD | 193.07 | 359.69 | 2716.20 | - |
| | SE | 6.94 | 12.95 | 102.01 | - |
| | Median | 15.00 | -30.00 | -75.00 | - |
| | 95% lclm | 50.66 | -134.87 | -123.25 | - |
| | 95% uclm | 77.89 | -84.05 | 277.31 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1440.00 | 71900.00 | - |
| | 25th percentile | 0.00 | -90.00 | -100.00 | - |
| | 75th percentile | 60.00 | 0.00 | -42.86 | - |
| Week 28 | N | 772 | 770 | 709 | <0.0001 |
| | Mean | 63.40 | -114.19 | -17.23 | - |
| | SD | 200.94 | 363.10 | 588.02 | - |
| | SE | 7.23 | 13.09 | 22.08 | - |
| | Median | 10.00 | -30.00 | -83.33 | - |
| | 95% lclm | 49.20 | -139.88 | -60.59 | - |
| | 95% uclm | 77.60 | -88.51 | 26.13 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1440.00 | 14300.00 | - |
| | 25th percentile | 0.00 | -105.00 | -100.00 | - |
| | 75th percentile | 33.50 | -5.00 | -50.00 | - |
| Week 36 | N | 749 | 747 | 688 | <0.0001 |
| | Mean | 48.76 | -127.83 | -37.74 | - |
| | SD | 165.23 | 339.75 | 327.66 | - |
| | SE | 6.04 | 12.43 | 12.49 | - |
| | Median | 10.00 | -45.00 | -84.80 | - |
| | 95% lclm | 36.91 | -152.23 | -62.27 | - |
| | 95% uclm | 60.61 | -103.42 | -13.22 | - |
| | Min | 0.00 | -1440.00 | -100.00 | - |
| | Max | 1440.00 | 1410.00 | 4700.00 | - |
| | 25th percentile | 0.00 | -120.00 | -100.00 | - |
| | 75th percentile | 30.00 | -10.00 | -50.00 | - |

Percent Change from Baseline =100*(observed value – baseline value)/baseline value.
lclm = lower confidence level limit; min = minimum, max = maximum; mITT = modified intent to treat
N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean duration of morning stiffness (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 23). The difference between the E50+M and E25+M treatment groups in the adjusted mean duration of morning stiffness change from Period 2 baseline at Week 88 was not statistically significant.

**Table 23. Change From Period 2 Baseline in Duration of Morning Stiffness (Minutes) (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI) [b] |
| Week 40 | 191 | 3.43 (12.82) | 198 | 14.00 (12.60) | 190 | 45.10 (12.83) | E50+M | PBO+M | 0.0214 | -41.67 (-77.1, -6.2) |
| | | | | | | | E50+M | E25+M | 0.5544 | -10.57 (-45.6, 24.5) |
| | | | | | | | E25+M | PBO+M | 0.0826 | -31.10 (-66.2, 4.0) |
| Week 48 | 200 | -7.64 (14.47) | 201 | 35.54 (14.47) | 196 | 72.41 (14.62) | E50+M | PBO+M | 0.0001 | -80.05 (-120.3, -39.8) |
| | | | | | | | E50+M | E25+M | 0.0344 | -43.18 (-83.2, -3.2) |
| | | | | | | | E25+M | PBO+M | 0.0721 | -36.87 (-77.1, 3.3) |
| Week 56 | 200 | -2.10 (14.19) | 201 | 24.04 (14.19) | 196 | 87.09 (14.34) | E50+M | PBO+M | <0.0001 | -89.19 (-128.7, -49.7) |
| | | | | | | | E50+M | E25+M | 0.1910 | -26.14 (-65.4, 13.1) |
| | | | | | | | E25+M | PBO+M | 0.0018 | -63.05 (-102.5, -23.6) |
| Week 64 | 200 | 13.80 (16.09) | 201 | 15.65 (16.10) | 196 | 98.16 (16.26) | E50+M | PBO+M | 0.0002 | -84.36 (-129.1, -39.6) |
| | | | | | | | E50+M | E25+M | 0.9350 | -1.85 (-46.3, 42.6) |
| | | | | | | | E25+M | PBO+M | 0.0003 | -82.52 (-127.2, -37.8) |
| Week 72 | 200 | 8.30 (17.36) | 201 | 18.50 (17.37) | 196 | 117.04 (17.54) | E50+M | PBO+M | <0.0001 | -108.73 (-157.0, -60.4) |
| | | | | | | | E50+M | E25+M | 0.6764 | -10.20 (-58.2, 37.8) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -98.53 (-146.7, -50.3) |
| Week 80 | 200 | -1.06 (15.18) | 201 | 12.63 (15.18) | 196 | 114.42 (15.34) | E50+M | PBO+M | <0.0001 | -115.48 (-157.7, -73.3) |
| | | | | | | | E50+M | E25+M | 0.5219 | -13.69 (-55.6, 28.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -101.80 (-144.0, -59.6) |
| Week 88 | 200 | 24.54 (16.29) | 201 | 12.23 (16.30) | 196 | 96.14 (16.46) | E50+M | PBO+M | 0.0020 | -71.60 (-116.9, -26.3) |
| | | | | | | | E50+M | E25+M | 0.5917 | 12.30 (-32.7, 57.3) |
| | | | | | | | E25+M | PBO+M | 0.0003 | -83.91 (-129.2, -38.7) |

Negative values for stiffness found in data were imputed to missing.
ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.
b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

Painful and Swollen Joints: For the observed case analysis, improvements in swollen joint counts are summarized in Table 24, and improvements in tender joint counts are summarized in Table 25. For swollen joint counts, the mean percent improvement from Baseline at Week 36 was 74.82%, while for tender joint counts the mean percent improvement from Baseline at Week 36 was 70.68%.

**Table 24. Descriptive Summary for Prorated Swollen Joint Counts During Period 1 in the mITT Population (Observed Cases) 0–28 Joints**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 830 | - | - | - |
| | Mean | 3.82 | - | - | - |
| | SD | 2.60 | - | - | - |
| | SE | 0.09 | - | - | - |
| | Median | 3.17 | - | - | - |
| | 95% lclm | 3.64 | - | - | - |
| | 95% uclm | 3.99 | - | - | - |
| | Min | 0.00 | - | - | - |
| | Max | 17.00 | - | - | - |
| | 25th percentile | 2.00 | - | - | - |
| | 75th percentile | 5.00 | - | - | - |
| Week 4 | N | 792 | 790 | 758 | <0.0001 |
| | Mean | 2.53 | -1.31 | -31.23 | - |
| | SD | 2.46 | 2.28 | 73.15 | - |
| | SE | 0.09 | 0.08 | 2.66 | - |
| | Median | 2.00 | -1.00 | -40.00 | - |
| | 95% lclm | 2.36 | -1.47 | -36.45 | - |
| | 95% uclm | 2.70 | -1.15 | -26.02 | - |
| | Min | 0.00 | -11.00 | -100.00 | - |
| | Max | 13.00 | 10.00 | 900.00 | - |
| | 25th percentile | 1.00 | -2.00 | -66.67 | - |
| | 75th percentile | 4.00 | 0.00 | 0.00 | - |
| Week 8 | N | 792 | 790 | 758 | <0.0001 |
| | Mean | 1.80 | -1.99 | -52.36 | - |
| | SD | 2.20 | 2.30 | 58.96 | - |
| | SE | 0.08 | 0.08 | 2.14 | - |
| | Median | 1.00 | -2.00 | -60.00 | - |
| | 95% lclm | 1.65 | -2.15 | -56.56 | - |
| | 95% uclm | 1.96 | -1.83 | -48.15 | - |
| | Min | 0.00 | -14.00 | -100.00 | - |
| | Max | 15.00 | 11.00 | 700.00 | - |
| | 25th percentile | 0.00 | -3.00 | -100.00 | - |
| | 75th percentile | 3.00 | -1.00 | -25.00 | - |
| Week 12 | N | 789 | 787 | 756 | <0.0001 |
| | Mean | 1.44 | -2.35 | -62.87 | - |
| | SD | 2.02 | 2.35 | 51.08 | - |
| | SE | 0.07 | 0.08 | 1.86 | - |
| | Median | 1.00 | -2.00 | -75.00 | - |
| | 95% lclm | 1.30 | -2.52 | -66.52 | - |
| | 95% uclm | 1.59 | -2.19 | -59.22 | - |
| | Min | 0.00 | -16.00 | -100.00 | - |
| | Max | 15.00 | 10.00 | 400.00 | - |

**Table 24. Descriptive Summary for Prorated Swollen Joint Counts During Period 1 in the mITT Population (Observed Cases) 0–28 Joints**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | 25th percentile | 0.00 | -3.11 | -100.00 | - |
| | 75th percentile | 2.00 | -1.00 | -45.30 | - |
| Week 20 | N | 790 | 788 | 759 | <0.0001 |
| | Mean | 1.16 | -2.67 | -67.69 | - |
| | SD | 1.98 | 2.70 | 64.11 | - |
| | SE | 0.07 | 0.10 | 2.33 | - |
| | Median | 0.00 | -2.07 | -100.00 | - |
| | 95% lclm | 1.02 | -2.86 | -72.25 | - |
| | 95% uclm | 1.30 | -2.48 | -63.12 | - |
| | Min | 0.00 | -15.00 | -100.00 | - |
| | Max | 17.00 | 12.00 | 550.00 | - |
| | 25th percentile | 0.00 | -4.00 | -100.00 | - |
| | 75th percentile | 2.00 | -1.00 | -55.56 | - |
| Week 28 | N | 781 | 779 | 750 | <0.0001 |
| | Mean | 0.99 | -2.83 | -75.91 | - |
| | SD | 1.98 | 2.61 | 46.54 | - |
| | SE | 0.07 | 0.09 | 1.70 | - |
| | Median | 0.00 | -3.00 | -100.00 | - |
| | 95% lclm | 0.85 | -3.02 | -79.24 | - |
| | 95% uclm | 1.13 | -2.65 | -72.57 | - |
| | Min | 0.00 | -15.00 | -100.00 | - |
| | Max | 13.00 | 8.00 | 266.67 | - |
| | 25th percentile | 0.00 | -4.00 | -100.00 | - |
| | 75th percentile | 1.00 | -1.00 | -66.67 | - |
| Week 36 | N | 765 | 763 | 734 | <0.0001 |
| | Mean | 0.98 | -2.85 | -74.82 | - |
| | SD | 2.02 | 2.66 | 54.36 | - |
| | SE | 0.07 | 0.10 | 2.01 | - |
| | Median | 0.00 | -3.00 | -100.00 | - |
| | 95% lclm | 0.84 | -3.04 | -78.76 | - |
| | 95% uclm | 1.13 | -2.67 | -70.88 | - |
| | Min | 0.00 | -14.00 | -100.00 | - |
| | Max | 17.00 | 12.00 | 500.00 | - |
| | 25th percentile | 0.00 | -4.00 | -100.00 | - |
| | 75th percentile | 1.00 | -1.00 | -66.67 | - |

Percent Change from Baseline =100* (observed value – baseline value) / baseline value.
lclm = lower confidence level limit; min = minimum, max = maximum; mITT = modified intent to treat
N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

**Table 25. Descriptive Summary for Prorated Tender Joint Counts During Period 1 in the mITT Population (Observed Cases) 0-28 Joints**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 830 | - | - | - |
| | Mean | 5.09 | - | - | - |
| | SD | 2.88 | - | - | - |
| | SE | 0.10 | - | - | - |
| | Median | 5.00 | - | - | - |
| | 95% lclm | 4.90 | - | - | - |
| | 95% uclm | 5.29 | - | - | - |
| | Min | 0.00 | - | - | - |
| | Max | 21.00 | - | - | - |
| | 25th percentile | 3.00 | - | - | - |
| | 75th percentile | 6.00 | - | - | - |
| Week 4 | N | 792 | 790 | 779 | <0.0001 |
| | Mean | 3.40 | -1.68 | -29.56 | - |
| | SD | 3.25 | 2.94 | 89.90 | - |
| | SE | 0.12 | 0.10 | 3.22 | - |
| | Median | 3.00 | -2.00 | -40.00 | - |
| | 95% lclm | 3.17 | -1.89 | -35.88 | - |
| | 95% uclm | 3.63 | -1.48 | -23.23 | - |
| | Min | 0.00 | -14.00 | -100.00 | - |
| | Max | 22.00 | 20.00 | 1700.00 | - |
| | 25th percentile | 1.00 | -3.00 | -66.67 | - |
| | 75th percentile | 4.00 | 0.00 | 0.00 | - |
| Week 8 | N | 792 | 790 | 780 | <0.0001 |
| | Mean | 2.53 | -2.57 | -48.13 | - |
| | SD | 2.79 | 2.86 | 56.87 | - |
| | SE | 0.10 | 0.10 | 2.04 | - |
| | Median | 2.00 | -2.00 | -60.00 | - |
| | 95% lclm | 2.33 | -2.77 | -52.13 | - |
| | 95% uclm | 2.72 | -2.37 | -44.13 | - |
| | Min | 0.00 | -16.00 | -100.00 | - |
| | Max | 25.00 | 11.00 | 500.00 | - |
| | 25th percentile | 1.00 | -4.00 | -87.50 | - |
| | 75th percentile | 4.00 | -1.00 | -25.00 | - |
| Week 12 | N | 789 | 787 | 776 | <0.0001 |
| | Mean | 2.17 | -2.91 | -54.13 | - |
| | SD | 2.97 | 3.22 | 79.85 | - |
| | SE | 0.11 | 0.11 | 2.87 | - |
| | Median | 1.00 | -3.00 | -66.67 | - |
| | 95% lclm | 1.96 | -3.13 | -59.76 | - |
| | 95% uclm | 2.38 | -2.68 | -48.51 | - |
| | Min | 0.00 | -19.00 | -100.00 | - |
| | Max | 27.00 | 25.00 | 1250.00 | - |
| | 25th percentile | 0.00 | -4.00 | -100.00 | - |
| | 75th percentile | 3.00 | -1.00 | -39.23 | - |
| Week 20 | N | 790 | 788 | 777 | <0.0001 |
| | Mean | 1.91 | -3.17 | -57.79 | - |
| | SD | 2.84 | 3.48 | 74.91 | - |
| | SE | 0.10 | 0.12 | 2.69 | - |
| | Median | 1.00 | -3.00 | -75.00 | - |

**Table 25. Descriptive Summary for Prorated Tender Joint Counts During Period 1 in the mITT Population (Observed Cases) 0-28 Joints**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | 95% lclm | 1.71 | -3.41 | -63.07 | - |
| | 95% uclm | 2.10 | -2.93 | -52.52 | - |
| | Min | 0.00 | -21.00 | -100.00 | - |
| | Max | 24.00 | 20.00 | 900.00 | - |
| | 25th percentile | 0.00 | -5.00 | -100.00 | - |
| | 75th percentile | 2.00 | -2.00 | -50.00 | - |
| Week 28 | N | 781 | 779 | 768 | <0.0001 |
| | Mean | 1.59 | -3.47 | -65.08 | - |
| | SD | 2.53 | 3.32 | 62.98 | - |
| | SE | 0.09 | 0.12 | 2.27 | - |
| | Median | 1.00 | -4.00 | -83.33 | - |
| | 95% lclm | 1.41 | -3.70 | -69.54 | - |
| | 95% uclm | 1.77 | -3.24 | -60.61 | - |
| | Min | 0.00 | -21.00 | -100.00 | - |
| | Max | 22.00 | 18.00 | 500.00 | - |
| | 25th percentile | 0.00 | -5.00 | -100.00 | - |
| | 75th percentile | 2.00 | -2.00 | -50.00 | - |
| Week 36 | N | 765 | 763 | 752 | <0.0001 |
| | Mean | 1.31 | -3.75 | -70.68 | - |
| | SD | 2.42 | 3.36 | 64.24 | - |
| | SE | 0.09 | 0.12 | 2.34 | - |
| | Median | 0.00 | -4.00 | -100.00 | - |
| | 95% lclm | 1.13 | -3.99 | -75.28 | - |
| | 95% uclm | 1.48 | -3.51 | -66.08 | - |
| | Min | 0.00 | -20.00 | -100.00 | - |
| | Max | 23.00 | 20.00 | 666.67 | - |
| | 25th percentile | 0.00 | -5.00 | -100.00 | - |
| | 75th percentile | 2.00 | -2.00 | -66.67 | - |

Percent Change from Baseline =100* (observed value – baseline value) / baseline value.
lclm = lower confidence level limit; max = maximum; min = minimum; mITT = modified intent to treat; N = number of subjects; SD = standard deviation, SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean swollen joint count (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 25). The difference between the E50+M and E25+M treatment groups in the adjusted mean swollen joint count change from Period 2 Baseline at Week 88 was not statistically significant.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean tender joint count (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 26). The difference between the E50+M and E25+M treatment groups in the adjusted mean tender joint count change from Period 2 Baseline at Week 88 was not statistically significant.

**Table 25. Change From Period 2 Baseline in Swollen Joint Count (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 0.10 (0.11) | 197 | 0.14 (0.11) | 188 | 0.91 (0.11) | E50+M | PBO+M | <0.0001 | -0.81 (-1.1, -0.5) |
| | | | | | | | E50+M | E25+M | 0.8015 | -0.04 (-0.3, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.78 (-1.1, -0.5) |
| Week 48 | 201 | 0.25 (0.15) | 201 | 0.21 (0.15) | 197 | 1.38 (0.15) | E50+M | PBO+M | <0.0001 | -1.14 (-1.5, -0.7) |
| | | | | | | | E50+M | E25+M | 0.8534 | 0.04 (-0.4, 0.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.18 (-1.6, -0.8) |
| Week 56 | 201 | 0.28 (0.16) | 201 | 0.26 (0.16) | 197 | 1.49 (0.16) | E50+M | PBO+M | <0.0001 | -1.21 (-1.7, -0.8) |
| | | | | | | | E50+M | E25+M | 0.9074 | 0.03 (-0.4, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.24 (-1.7, -0.8) |
| Week 64 | 201 | 0.37 (0.17) | 201 | 0.34 (0.17) | 197 | 1.64 (0.17) | E50+M | PBO+M | <0.0001 | -1.28 (-1.8, -0.8) |
| | | | | | | | E50+M | E25+M | 0.9229 | 0.02 (-0.4, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.30 (-1.8, -0.8) |
| Week 72 | 201 | 0.20 (0.16) | 201 | 0.22 (0.16) | 197 | 1.64 (0.17) | E50+M | PBO+M | <0.0001 | -1.44 (-1.9, -1.0) |
| | | | | | | | E50+M | E25+M | 0.9279 | -0.02 (-0.5, 0.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.42 (-1.9, -1.0) |
| Week 80 | 201 | 0.25 (0.18) | 201 | 0.32 (0.18) | 197 | 1.82 (0.18) | E50+M | PBO+M | <0.0001 | -1.58 (-2.1, -1.1) |
| | | | | | | | E50+M | E25+M | 0.7695 | -0.07 (-0.6, 0.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.50 (-2.0, -1.0) |
| Week 88 | 201 | 0.17 (0.18) | 201 | 0.49 (0.18) | 197 | 1.92 (0.18) | E50+M | PBO+M | <0.0001 | -1.75 (-2.3, -1.2) |
| | | | | | | | E50+M | E25+M | 0.2182 | -0.31 (-0.8, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.44 (-1.9, -0.9) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome was independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

**Table 26. Change From Period 2 Baseline in Tender Joint Count (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 0.61 (0.17) | 197 | 0.49 (0.17) | 188 | 1.47 (0.17) | E50+M | PBO+M | 0.0003 | -0.86 (-1.3, -0.4) |
| | | | | | | | E50+M | E25+M | 0.6088 | 0.12 (-0.3, 0.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.98 (-1.4, -0.5) |
| Week 48 | 201 | 0.67 (0.21) | 201 | 0.63 (0.21) | 197 | 2.69 (0.21) | E50+M | PBO+M | <0.0001 | -2.02 (-2.6, -1.4) |
| | | | | | | | E50+M | E25+M | 0.9048 | 0.04 (-0.5, 0.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.06 (-2.6, -1.5) |
| Week 56 | 201 | 0.61 (0.20) | 201 | 0.66 (0.20) | 197 | 2.67 (0.21) | E50+M | PBO+M | <0.0001 | -2.06 (-2.6, -1.5) |
| | | | | | | | E50+M | E25+M | 0.8437 | -0.06 (-0.6, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.00 (-2.6, -1.4) |
| Week 64 | 201 | 0.79 (0.22) | 201 | 0.73 (0.22) | 197 | 2.76 (0.22) | E50+M | PBO+M | <0.0001 | -1.98 (-2.6, -1.4) |
| | | | | | | | E50+M | E25+M | 0.8587 | 0.06 (-0.6, 0.7) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.03 (-2.6, -1.4) |
| Week 72 | 201 | 0.63 (0.23) | 201 | 0.78 (0.23) | 197 | 3.01 (0.23) | E50+M | PBO+M | <0.0001 | -2.38 (-3.0, -1.8) |
| | | | | | | | E50+M | E25+M | 0.6323 | -0.15 (-0.8, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.23 (-2.9, -1.6) |
| Week 80 | 201 | 0.74 (0.23) | 201 | 0.88 (0.23) | 197 | 3.02 (0.23) | E50+M | PBO+M | <0.0001 | -2.28 (-2.9, -1.6) |
| | | | | | | | E50+M | E25+M | 0.6558 | -0.15 (-0.8, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.14 (-2.8, -1.5) |
| Week 88 | 201 | 0.73 (0.24) | 201 | 0.78 (0.24) | 197 | 3.14 (0.24) | E50+M | PBO+M | <0.0001 | -2.41 (-3.1, -1.7) |
| | | | | | | | E50+M | E25+M | 0.8688 | -0.06 (-0.7, 0.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -2.35 (-3.0, -1.7) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome was independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

General Health VAS and Pain VAS: At Week 36, the mean percent reduction in the general health VAS was 46.96% (Table 27) and 56.64% for the pain VAS (Table 28) in the observed case analysis.

**Table 27. Descriptive Summary for General Health VAS During Period 1 in the mITT Population (Observed Cases) 0-100**

| Week | Statistics | Score E50/M[a] | Change From Baseline E50/M[a] | Percent Change From Baseline E50/M[a] | Within Group p-Value E50/M[a] |
|---|---|---|---|---|---|
| Baseline | N | 832 | - | - | - |
| | Mean | 43.37 | - | - | - |
| | SD | 16.95 | - | - | - |
| | SE | 0.59 | - | - | - |
| | Median | 44.00 | - | - | - |
| | 95% lclm | 42.21 | - | - | - |
| | 95% uclm | 44.52 | - | - | - |
| | Min | 0.00 | - | - | - |
| | Max | 98.00 | - | - | - |
| | 25th percentile | 31.00 | - | - | - |
| | 75th percentile | 53.00 | - | - | - |
| Week 4 | N | 788 | 786 | 785 | <0.0001 |
| | Mean | 33.90 | -9.39 | -9.52 | - |
| | SD | 17.85 | 18.93 | 163.21 | - |
| | SE | 0.64 | 0.68 | 5.83 | - |
| | Median | 33.00 | -9.00 | -20.97 | - |
| | 95% lclm | 32.65 | -10.71 | -20.95 | - |
| | 95% uclm | 35.15 | -8.06 | 1.92 | - |
| | Min | 0.00 | -84.00 | -100.00 | - |
| | Max | 100.00 | 70.00 | 4300.00 | - |
| | 25 percentile | 20.00 | -20.00 | -47.83 | - |
| | 75 percentile | 46.00 | 2.00 | 4.55 | - |
| Week 8 | N | 793 | 792 | 791 | <0.0001 |
| | Mean | 30.65 | -12.62 | -15.54 | - |
| | SD | 19.05 | 21.21 | 157.12 | - |
| | SE | 0.68 | 0.75 | 5.59 | - |
| | Median | 28.00 | -13.00 | -31.67 | - |
| | 95% lclm | 29.33 | -14.10 | -26.50 | - |
| | 95% uclm | 31.98 | -11.14 | -4.57 | - |
| | Min | 0.00 | -82.00 | -100.00 | - |
| | Max | 98.00 | 87.00 | 3800.00 | - |
| | 25th percentile | 16.00 | -26.00 | -58.82 | - |
| | 75th percentile | 44.00 | -1.00 | -3.70 | - |
| Week 12 | N | 791 | 790 | 789 | <0.0001 |
| | Mean | 26.89 | -16.07 | -28.92 | - |
| | SD | 18.29 | 20.37 | 89.80 | - |
| | SE | 0.65 | 0.72 | 3.20 | - |
| | Median | 23.00 | -16.00 | -42.86 | - |
| | 95% lclm | 25.61 | -17.50 | -35.20 | - |
| | 95% uclm | 28.16 | -14.65 | -22.65 | - |
| | Min | 0.00 | -80.00 | -100.00 | - |
| | Max | 87.00 | 63.00 | 1900.00 | - |
| | 25th percentile | 12.00 | -29.00 | -66.67 | - |
| | 75th percentile | 38.00 | -4.00 | -11.48 | - |

## Table 27. Descriptive Summary for General Health VAS During Period 1 in the mITT Population (Observed Cases) 0-100

| Week | Statistics | Score E50/M[a] | Change From Baseline E50/M[a] | Percent Change From Baseline E50/M[a] | Within Group p-Value E50/M[a] |
|---|---|---|---|---|---|
| Week 20 | N | 788 | 787 | 786 | <0.0001 |
| | Mean | 23.81 | -19.39 | -31.30 | - |
| | SD | 18.56 | 20.51 | 259.94 | - |
| | SE | 0.66 | 0.73 | 9.27 | - |
| | Median | 18.00 | -20.00 | -51.86 | - |
| | 95% lclm | 22.51 | -20.83 | -49.50 | - |
| | 95% uclm | 25.10 | -17.96 | -13.10 | - |
| | Min | 0.00 | -79.00 | -100.00 | - |
| | Max | 96.00 | 71.00 | 7100.00 | - |
| | 25th percentile | 9.00 | -33.00 | -75.00 | - |
| | 75th percentile | 34.50 | -7.00 | -18.29 | - |
| Week 28 | N | 780 | 779 | 778 | <0.0001 |
| | Mean | 22.30 | -20.57 | -36.30 | - |
| | SD | 20.20 | 21.79 | 241.41 | - |
| | SE | 0.72 | 0.78 | 8.65 | - |
| | Median | 15.00 | -22.00 | -60.99 | - |
| | 95% lclm | 20.88 | -22.11 | -53.29 | - |
| | 95% uclm | 23.72 | -19.04 | -19.31 | - |
| | Min | 0.00 | -80.00 | -100.00 | - |
| | Max | 97.00 | 65.00 | 6500.00 | - |
| | 25th percentile | 8.00 | -34.00 | -80.00 | - |
| | 75th percentile | 32.00 | -8.00 | -23.53 | - |
| Week 36 | N | 765 | 764 | 763 | <0.0001 |
| | Mean | 18.54 | -24.20 | -46.96 | - |
| | SD | 18.34 | 21.20 | 160.58 | - |
| | SE | 0.66 | 0.77 | 5.81 | - |
| | Median | 12.00 | -26.00 | -69.39 | - |
| | 95% lclm | 17.24 | -25.70 | -58.37 | - |
| | 95% uclm | 19.84 | -22.69 | -35.55 | - |
| | Min | 0.00 | -82.00 | -100.00 | - |
| | Max | 92.00 | 63.00 | 4100.00 | - |
| | 25th percentile | 5.00 | -39.00 | -87.10 | - |
| | 75th percentile | 28.00 | -12.00 | -32.61 | - |

Percent change from Baseline =100*(observed value – baseline value)/baseline value.
lclm = lower confidence level limit; min = minimum; mITT = modified intent to treat; max = maximum; N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit; VAS = visual analog scale.
a. E50+M = Etanercept 50 mg + Methotrexate.

## Table 28. Descriptive Summary for Pain VAS during Period 1 in the mITT Population (Observed Cases) 0-100

| Week | Statistics | Score E50/M[a] | Change From Baseline E50/M[a] | Percent Change From Baseline E50/M[a] | Within Group p-Value E50/M[a] |
|---|---|---|---|---|---|
| Baseline | N | 832 | - | - | - |
| | Mean | 45.47 | - | - | - |
| | SD | 17.39 | - | - | - |
| | SE | 0.60 | - | - | - |
| | Median | 46.00 | - | - | - |
| | 95% lclm | 44.29 | - | - | - |
| | 95% uclm | 46.65 | - | - | - |
| | Min | 0.00 | - | - | - |
| | Max | 97.00 | - | - | - |
| | 25th percentile | 32.50 | - | - | - |
| | 75th percentile | 57.00 | - | - | - |
| Week 4 | N | 788 | 786 | 784 | <0.0001 |
| | Mean | 32.25 | -13.06 | -22.27 | - |
| | SD | 18.99 | 19.43 | 62.96 | - |
| | SE | 0.68 | 0.69 | 2.25 | - |
| | Median | 30.50 | -11.00 | -28.06 | - |
| | 95% lclm | 30.93 | -14.42 | -26.68 | - |
| | 95% uclm | 33.58 | -11.70 | -17.85 | - |
| | Min | 0.00 | -87.00 | -100.00 | - |
| | Max | 100.00 | 52.00 | 1050.00 | - |
| | 25th percentile | 18.00 | -25.00 | -56.43 | - |
| | 75th percentile | 45.00 | -1.00 | -1.77 | - |
| Week 8 | N | 793 | 792 | 790 | <0.0001 |
| | Mean | 27.98 | -17.43 | -27.77 | - |
| | SD | 19.24 | 20.74 | 119.45 | - |
| | SE | 0.68 | 0.74 | 4.25 | - |
| | Median | 25.00 | -17.00 | -39.88 | - |
| | 95% lclm | 26.64 | -18.88 | -36.11 | - |
| | 95% uclm | 29.33 | -15.98 | -19.42 | - |
| | Min | 0.00 | -80.00 | -100.00 | - |
| | Max | 100.00 | 88.00 | 2200.00 | - |
| | 25th percentile | 13.00 | -30.00 | -67.44 | - |
| | 75th percentile | 39.00 | -5.00 | -12.50 | - |
| Week 12 | N | 791 | 790 | 788 | <0.0001 |
| | Mean | 25.29 | -19.96 | -37.57 | - |
| | SD | 19.15 | 20.92 | 81.59 | - |
| | SE | 0.68 | 0.74 | 2.91 | - |
| | Median | 21.00 | -19.00 | -50.00 | - |
| | 95% lclm | 23.95 | -21.42 | -43.27 | - |
| | 95% uclm | 26.62 | -18.49 | -31.86 | - |
| | Min | 0.00 | -80.00 | -100.00 | - |
| | Max | 86.00 | 63.00 | 1700.00 | - |
| | 25th percentile | 10.00 | -34.00 | -75.00 | - |
| | 75th percentile | 37.00 | -8.00 | -17.52 | - |
| Week 20 | N | 787 | 786 | 784 | <0.0001 |
| | Mean | 22.67 | -22.69 | -46.04 | - |
| | SD | 19.16 | 20.94 | 51.12 | - |
| | SE | 0.68 | 0.75 | 1.83 | - |
| | Median | 18.00 | -24.00 | -58.82 | - |

**Table 28. Descriptive Summary for Pain VAS during Period 1 in the mITT Population (Observed Cases) 0-100**

| Week | Statistics | Score E50/M[a] | Change From Baseline E50/M[a] | Percent Change From Baseline E50/M[a] | Within Group p-Value E50/M[a] |
|---|---|---|---|---|---|
| | 95% lclm | 21.33 | -24.16 | -49.62 | - |
| | 95% uclm | 24.01 | -21.23 | -42.46 | - |
| | Min | 0.00 | -82.00 | -100.00 | - |
| | Max | 98.00 | 58.00 | 500.00 | - |
| | 25th percentile | 8.00 | -36.00 | -80.00 | - |
| | 75th percentile | 32.00 | -9.00 | -22.20 | - |
| Week 28 | N | 780 | 779 | 777 | <0.0001 |
| | Mean | 21.12 | -24.10 | -47.17 | - |
| | SD | 19.79 | 22.08 | 88.57 | - |
| | SE | 0.71 | 0.79 | 3.18 | - |
| | Median | 14.00 | -25.00 | -64.29 | - |
| | 95% lclm | 19.73 | -25.65 | -53.41 | - |
| | 95% uclm | 22.51 | -22.55 | -40.93 | - |
| | Min | 0.00 | -86.00 | -100.00 | - |
| | Max | 97.00 | 78.00 | 1950.00 | - |
| | 25th percentile | 6.00 | -40.00 | -84.62 | - |
| | 75th percentile | 30.50 | -10.00 | -28.57 | - |
| Week 36 | N | 765 | 764 | 762 | <0.0001 |
| | Mean | 17.50 | -27.58 | -56.64 | - |
| | SD | 18.13 | 21.06 | 59.56 | - |
| | SE | 0.66 | 0.76 | 2.16 | - |
| | Median | 10.00 | -29.00 | -74.36 | - |
| | 95% lclm | 16.22 | -29.07 | -60.87 | - |
| | 95% uclm | 18.79 | -26.08 | -52.40 | - |
| | Min | 0.00 | -82.00 | -100.00 | - |
| | Max | 93.00 | 52.00 | 700.00 | - |
| | 25th percentile | 4.00 | -42.00 | -90.63 | - |
| | 75th percentile | 26.00 | -14.00 | -38.20 | - |

Percent Change from Baseline =100 * (observed value – baseline value) / baseline value.
lclm = lower confidence level limit; min = minimum; max = maximum; mITT = modified intent to treat; N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit; VAS = visual analog scale.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean general health VAS scores (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 29). The difference between the E50+M and E25+M treatment groups in the adjusted mean general health VAS score change from Period 2 Baseline at Week 88 was not statistically significant.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean pain VAS scores (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 30). The difference between the E50+M and E25+M treatment groups in the adjusted mean pain VAS score change from Period 2 Baseline at Week 88 was not statistically significant.

**Table 29. Change From Period 2 Baseline in General Health VAS Score (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 3.26 (1.12) | 198 | 5.82 (1.11) | 192 | 12.05 (1.13) | E50+M | PBO+M | <0.0001 | -8.79 (-11.9, -5.7) |
| | | | | | | | E50+M | E25+M | 0.1033 | -2.55 (-5.6, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -6.23 (-9.3, -3.1) |
| Week 48 | 201 | 4.67 (1.19) | 201 | 5.36 (1.20) | 197 | 16.76 (1.21) | E50+M | PBO+M | <0.0001 | -12.09 (-15.4, -8.8) |
| | | | | | | | E50+M | E25+M | 0.6802 | -0.69 (-4.0, 2.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -11.39 (-14.7, -8.1) |
| Week 56 | 201 | 5.09 (1.25) | 201 | 6.46 (1.26) | 197 | 17.19 (1.27) | E50+M | PBO+M | <0.0001 | -12.09 (-15.6, -8.6) |
| | | | | | | | E50+M | E25+M | 0.4404 | -1.36 (-4.8, 2.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -10.73 (-14.2, -7.2) |
| Week 64 | 201 | 4.04 (1.22) | 201 | 5.36 (1.22) | 197 | 16.87 (1.23) | E50+M | PBO+M | <0.0001 | -12.83 (-16.2, -9.4) |
| | | | | | | | E50+M | E25+M | 0.4437 | -1.32 (-4.7, 2.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -11.51 (-14.9, -8.1) |
| Week 72 | 201 | 3.76 (1.33) | 201 | 6.88 (1.33) | 197 | 18.55 (1.34) | E50+M | PBO+M | <0.0001 | -14.79 (-18.5, -11.1) |
| | | | | | | | E50+M | E25+M | 0.0960 | -3.12 (-6.8, 0.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -11.67 (-15.4, -8.0) |
| Week 80 | 201 | 2.70 (1.28) | 201 | 4.59 (1.28) | 197 | 17.26 (1.29) | E50+M | PBO+M | <0.0001 | -14.56 (-18.1, -11.0) |
| | | | | | | | E50+M | E25+M | 0.2948 | -1.88 (-5.4, 1.6) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -12.68 (-16.2, -9.1) |
| Week 88 | 201 | 3.89 (1.33) | 201 | 6.22 (1.33) | 197 | 17.06 (1.34) | E50+M | PBO+M | <0.0001 | -13.16 (-16.9, -9.5) |
| | | | | | | | E50+M | E25+M | 0.2130 | -2.33 (-6.0, 1.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -10.83 (-14.5, -7.1) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error; VAS = visual analog scale.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

**Table 30. Change From Period 2 Baseline in Pain VAS Score (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 4.50 (1.15) | 198 | 4.91 (1.15) | 192 | 13.05 (1.17) | E50+M | PBO+M | <0.0001 | -8.55 (-11.8, -5.3) |
| | | | | | | | E50+M | E25+M | 0.8033 | -0.40 (-3.6, 2.8) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -8.14 (-11.3, -4.9) |
| Week 48 | 201 | 5.16 (1.29) | 201 | 5.66 (1.30) | 197 | 18.77 (1.31) | E50+M | PBO+M | <0.0001 | -13.61 (-17.2, -10.0) |
| | | | | | | | E50+M | E25+M | 0.7830 | -0.50 (-4.1, 3.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -13.11 (-16.7, -9.5) |
| Week 56 | 201 | 5.23 (1.29) | 201 | 6.25 (1.29) | 197 | 17.76 (1.30) | E50+M | PBO+M | <0.0001 | -12.53 (-16.1, -8.9) |
| | | | | | | | E50+M | E25+M | 0.5732 | -1.02 (-4.6, 2.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -11.50 (-15.1, -7.9) |
| Week 64 | 201 | 4.61 (1.32) | 201 | 6.55 (1.32) | 197 | 18.49 (1.33) | E50+M | PBO+M | <0.0001 | -13.88 (-17.6, -10.2) |
| | | | | | | | E50+M | E25+M | 0.2972 | -1.94 (-5.6, 1.7) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -11.94 (-15.6, -8.3) |
| Week 72 | 201 | 4.26 (1.37) | 201 | 7.05 (1.37) | 197 | 19.90 (1.38) | E50+M | PBO+M | <0.0001 | -15.64 (-19.4, -11.8) |
| | | | | | | | E50+M | E25+M | 0.1477 | -2.80 (-6.6, 1.0) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -12.85 (-16.6, -9.0) |
| Week 80 | 201 | 3.36 (1.36) | 201 | 5.92 (1.36) | 197 | 18.23 (1.37) | E50+M | PBO+M | <0.0001 | -14.87 (-18.6, -11.1) |
| | | | | | | | E50+M | E25+M | 0.1808 | -2.56 (-6.3, 1.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -12.31 (-16.1, -8.5) |
| Week 88 | 201 | 3.88 (1.37) | 201 | 6.31 (1.37) | 197 | 18.57 (1.39) | E50+M | PBO+M | <0.0001 | -14.70 (-18.5, -10.9) |
| | | | | | | | E50+M | E25+M | 0.2077 | -2.44 (-6.2, 1.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -12.26 (-16.1, -8.5) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error; VAS = visual analog scale.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

Physician Global Assessment: At Week 36, the mean percent reduction in physician global assessment in the observed case analysis was 64.16% (Table 31).

**Table 31: Descriptive Summary for Physician Global Assessment During Period 1 in the mITT Population (Observed Cases) 0–10**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 833 | - | - | - |
| | Mean | 4.11 | - | - | - |
| | SD | 1.32 | - | - | - |
| | SE | 0.05 | - | - | - |
| | Median | 4.00 | - | - | - |
| | 95% lclm | 4.02 | - | - | - |
| | 95% uclm | 4.20 | - | - | - |
| | Min | 1.00 | - | - | - |
| | Max | 8.00 | - | - | - |
| | 25th percentile | 3.00 | - | - | - |
| | 75th percentile | 5.00 | - | - | - |
| Week 4 | N | 787 | 786 | 786 | <0.0001 |
| | Mean | 2.81 | -1.29 | -27.78 | - |
| | SD | 1.32 | 1.47 | 38.41 | - |
| | SE | 0.05 | 0.05 | 1.37 | - |
| | Median | 3.00 | -1.00 | -33.33 | - |
| | 95% lclm | 2.72 | -1.39 | -30.47 | - |
| | 95% uclm | 2.90 | -1.19 | -25.09 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 10.00 | 8.00 | 400.00 | - |
| | 25th percentile | 2.00 | -2.00 | -50.00 | - |
| | 75th percentile | 4.00 | 0.00 | 0.00 | - |
| Week 8 | N | 788 | 788 | 788 | <0.0001 |
| | Mean | 2.22 | -1.88 | -41.91 | - |
| | SD | 1.31 | 1.64 | 39.02 | - |
| | SE | 0.05 | 0.06 | 1.39 | - |
| | Median | 2.00 | -2.00 | -50.00 | - |
| | 95% lclm | 2.13 | -2.00 | -44.64 | - |
| | 95% uclm | 2.31 | -1.77 | -39.18 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 8.00 | 6.00 | 300.00 | - |
| | 25th percentile | 1.00 | -3.00 | -66.67 | - |
| | 75th percentile | 3.00 | -1.00 | -25.00 | - |
| Week 12 | N | 783 | 783 | 783 | <0.0001 |
| | Mean | 1.95 | -2.15 | -48.88 | - |
| | SD | 1.33 | 1.67 | 38.80 | - |
| | SE | 0.05 | 0.06 | 1.39 | - |
| | Median | 2.00 | -2.00 | -50.00 | - |
| | 95% lclm | 1.86 | -2.27 | -51.60 | - |
| | 95% uclm | 2.05 | -2.03 | -46.15 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 15.00 | 11.00 | 275.00 | - |
| | 25th percentile | 1.00 | -3.00 | -75.00 | - |
| | 75th percentile | 3.00 | -1.00 | -33.33 | - |
| Week 20 | N | 784 | 784 | 784 | <0.0001 |
| | Mean | 1.77 | -2.33 | -53.72 | - |

**Table 31: Descriptive Summary for Physician Global Assessment During Period 1 in the mITT Population (Observed Cases) 0–10**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | SD | 1.40 | 1.75 | 39.32 | - |
| | SE | 0.05 | 0.06 | 1.40 | - |
| | Median | 2.00 | -2.00 | -60.00 | - |
| | 95% lclm | 1.67 | -2.45 | -56.48 | - |
| | 95% uclm | 1.86 | -2.20 | -50.96 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 10.00 | 7.00 | 233.33 | - |
| | 25th percentile | 1.00 | -3.00 | -75.00 | - |
| | 75th percentile | 2.00 | -1.00 | -33.33 | - |
| Week 28 | N | 779 | 779 | 779 | <0.0001 |
| | Mean | 1.53 | -2.56 | -59.68 | - |
| | SD | 1.21 | 1.63 | 34.84 | - |
| | SE | 0.04 | 0.06 | 1.25 | - |
| | Median | 1.00 | -3.00 | -66.67 | - |
| | 95% lclm | 1.45 | -2.68 | -62.13 | - |
| | 95% uclm | 1.62 | -2.45 | -57.23 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 10.00 | 7.00 | 233.33 | - |
| | 25th percentile | 1.00 | -4.00 | -80.00 | - |
| | 75th percentile | 2.00 | -2.00 | -50.00 | - |
| Week 36 | N | 763 | 763 | 763 | <0.0001 |
| | Mean | 1.37 | -2.71 | -64.16 | - |
| | SD | 1.22 | 1.62 | 34.93 | - |
| | SE | 0.04 | 0.06 | 1.26 | - |
| | Median | 1.00 | -3.00 | -66.67 | - |
| | 95% lclm | 1.29 | -2.82 | -66.64 | - |
| | 95% uclm | 1.46 | -2.59 | -61.68 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 10.00 | 6.00 | 200.00 | - |
| | 25th percentile | 1.00 | -4.00 | -83.33 | - |
| | 75th percentile | 2.00 | -2.00 | -50.00 | - |

Percent change from Baseline =100 * (observed value – baseline value) / baseline value.
lclm = lower confidence level limit; min = minimum; max = maximum; mITT = modified intent to treat; N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean Physician Global Assessment scores (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 32). The difference between the E50+M and E25+M treatment groups in the adjusted mean Physician Global Assessment score change from Period 2 Baseline at Week 88 was not statistically significant.

**Table 32. Change From Period 2 Baseline in Physician Global Assessment Score (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI) [b] |
| Week 40 | 196 | 0.25 (0.09) | 196 | 0.24 (0.09) | 186 | 0.98 (0.09) | E50+M | PBO+M | <0.0001 | -0.73 (-1.0, -0.5) |
| | | | | | | | E50+M | E25+M | 0.9636 | 0.01 (-0.2, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.74 (-1.0, -0.5) |
| Week 48 | 201 | 0.37 (0.10) | 201 | 0.26 (0.11) | 197 | 1.48 (0.11) | E50+M | PBO+M | <0.0001 | -1.11 (-1.4, -0.8) |
| | | | | | | | E50+M | E25+M | 0.4605 | 0.11 (-0.2, 0.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.22 (-1.5, -0.9) |
| Week 56 | 201 | 0.37 (0.10) | 201 | 0.34 (0.10) | 197 | 1.49 (0.11) | E50+M | PBO+M | <0.0001 | -1.12 (-1.4, -0.8) |
| | | | | | | | E50+M | E25+M | 0.8404 | 0.03 (-0.3, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.15 (-1.4, -0.9) |
| Week 64 | 201 | 0.41 (0.11) | 201 | 0.26 (0.11) | 197 | 1.51 (0.11) | E50+M | PBO+M | <0.0001 | -1.10 (-1.4, -0.8) |
| | | | | | | | E50+M | E25+M | 0.3118 | 0.16 (-0.1, 0.5) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.26 (-1.6, -1.0) |
| Week 72 | 201 | 0.32 (0.11) | 201 | 0.24 (0.11) | 197 | 1.57 (0.11) | E50+M | PBO+M | <0.0001 | -1.26 (-1.6, -0.9) |
| | | | | | | | E50+M | E25+M | 0.6100 | 0.08 (-0.2, 0.4) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.34 (-1.6, -1.0) |
| Week 80 | 201 | 0.27 (0.11) | 201 | 0.34 (0.11) | 197 | 1.61 (0.11) | E50+M | PBO+M | <0.0001 | -1.34 (-1.6, -1.0) |
| | | | | | | | E50+M | E25+M | 0.6552 | -0.07 (-0.4, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.27 (-1.6, -1.0) |
| Week 88 | 201 | 0.23 (0.11) | 201 | 0.35 (0.12) | 197 | 1.67 (0.12) | E50+M | PBO+M | <0.0001 | -1.43 (-1.8, -1.1) |
| | | | | | | | E50+M | E25+M | 0.4753 | -0.12 (-0.4, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.32 (-1.6, -1.0) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

Subject Global Assessment: At Week 36, the mean percent reduction in subject global assessment in the observed case analysis was 51.01% (Table 33).

**Table 33. Descriptive Summary for Subject Global Assessment During Period 1 in the mITT Population (Observed Cases) 0-10**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| Baseline | N | 832 | - | - | - |
| | Mean | 4.85 | - | - | - |
| | SD | 1.72 | - | - | - |
| | SE | 0.06 | - | - | - |
| | Median | 5.00 | - | - | - |
| | 95% lclm | 4.74 | - | - | - |
| | 95% uclm | 4.97 | - | - | - |
| | Min | 1.00 | - | - | - |
| | Max | 10.00 | - | - | - |
| | 25th percentile | 4.00 | - | - | - |
| | 75th percentile | 6.00 | - | - | - |
| Week 4 | N | 788 | 786 | 786 | <0.0001 |
| | Mean | 3.67 | -1.16 | -19.70 | - |
| | SD | 1.72 | 1.76 | 37.51 | - |
| | SE | 0.06 | 0.06 | 1.34 | - |
| | Median | 4.00 | -1.00 | -25.00 | - |
| | 95% lclm | 3.55 | -1.29 | -22.33 | - |
| | 95% uclm | 3.79 | -1.04 | -17.08 | - |
| | Min | 0.00 | -9.00 | -100.00 | - |
| | Max | 10.00 | 5.00 | 200.00 | - |
| | 25th percentile | 2.50 | -2.00 | -40.00 | - |
| | 75th percentile | 5.00 | 0.00 | 0.00 | - |
| Week 8 | N | 793 | 792 | 792 | <0.0001 |
| | Mean | 3.35 | -1.48 | -25.54 | - |
| | SD | 1.79 | 1.97 | 48.30 | - |
| | SE | 0.06 | 0.07 | 1.72 | - |
| | Median | 3.00 | -1.00 | -33.33 | - |
| | 95% lclm | 3.23 | -1.62 | -28.91 | - |
| | 95% uclm | 3.48 | -1.34 | -22.17 | - |
| | Min | 0.00 | -8.00 | -100.00 | - |
| | Max | 10.00 | 7.00 | 700.00 | - |
| | 25th percentile | 2.00 | -3.00 | -50.00 | - |
| | 75th percentile | 4.00 | 0.00 | 0.00 | - |
| Week 12 | N | 791 | 790 | 790 | <0.0001 |
| | Mean | 3.12 | -1.70 | -30.74 | - |
| | SD | 1.89 | 2.08 | 48.15 | - |
| | SE | 0.07 | 0.07 | 1.71 | - |
| | Median | 3.00 | -2.00 | -33.33 | - |
| | 95% lclm | 2.99 | -1.84 | -34.10 | - |
| | 95% uclm | 3.25 | -1.55 | -27.37 | - |
| | Min | 0.00 | -10.00 | -100.00 | - |
| | Max | 10.00 | 6.00 | 600.00 | - |
| | 25th percentile | 2.00 | -3.00 | -66.67 | - |
| | 75th percentile | 4.00 | 0.00 | 0.00 | - |
| Week 20 | N | 788 | 787 | 787 | <0.0001 |

**Table 33. Descriptive Summary for Subject Global Assessment During Period 1 in the mITT Population (Observed Cases) 0-10**

| Week | Statistics | Score E50+M[a] | Change From Baseline E50+M[a] | Percent Change From Baseline E50+M[a] | Within Group p-Value E50+M[a] |
|---|---|---|---|---|---|
| | Mean | 2.76 | -2.06 | -38.98 | - |
| | SD | 1.89 | 2.13 | 43.34 | - |
| | SE | 0.07 | 0.08 | 1.54 | - |
| | Median | 2.00 | -2.00 | -50.00 | - |
| | 95% lclm | 2.63 | -2.21 | -42.01 | - |
| | 95% uclm | 2.90 | -1.92 | -35.95 | - |
| | Min | 0.00 | -9.00 | -100.00 | - |
| | Max | 10.00 | 5.00 | 250.00 | - |
| | 25th percentile | 1.00 | -3.00 | -66.67 | - |
| | 75th percentile | 4.00 | -1.00 | -20.00 | - |
| Week 28 | N | 780 | 779 | 779 | <0.0001 |
| | Mean | 2.57 | -2.24 | -43.89 | - |
| | SD | 1.94 | 2.12 | 41.34 | - |
| | SE | 0.07 | 0.08 | 1.48 | - |
| | Median | 2.00 | -2.00 | -50.00 | - |
| | 95% lclm | 2.44 | -2.39 | -46.80 | - |
| | 95% uclm | 2.71 | -2.09 | -40.98 | - |
| | Min | 0.00 | -9.00 | -100.00 | - |
| | Max | 10.00 | 5.00 | 166.67 | - |
| | 25th percentile | 1.00 | -4.00 | -75.00 | - |
| | 75th percentile | 3.00 | -1.00 | -25.00 | - |
| Week 36 | N | 765 | 764 | 764 | <0.0001 |
| | Mean | 2.22 | -2.59 | -51.01 | - |
| | SD | 1.86 | 2.16 | 43.23 | - |
| | SE | 0.07 | 0.08 | 1.56 | - |
| | Median | 2.00 | -3.00 | -66.67 | - |
| | 95% lclm | 2.09 | -2.74 | -54.08 | - |
| | 95% uclm | 2.35 | -2.43 | -47.94 | - |
| | Min | 0.00 | -10.00 | -100.00 | - |
| | Max | 10.00 | 6.00 | 250.00 | - |
| | 25th percentile | 1.00 | -4.00 | -75.00 | - |
| | 75th percentile | 3.00 | -1.00 | -33.33 | - |

Percent change from Baseline =100*(observed value – baseline value)/baseline value.
lclm = lower confidence level limit; min = minimum; max = maximum; mITT = modified intent to treat; N = number of subjects; SD = standard deviation; SE = standard error; uclm = upper confidence level limit.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the change from Period 2 Baseline in adjusted mean Subject Global Assessment scores (LOCF) were observed at Week 88 in favor of the E50+M and E25+M treatment groups when compared with the PBO+M treatment group (Table 34). The difference between the E50+M and E25+M treatment groups in the adjusted mean Subject Global Assessment score change from Period 2 Baseline at Week 88 was not statistically significant.

**Table 34. Change From Period 2 Baseline in Subject Global Assessment Score (LOCF): Comparison Between Treatment Groups During Period 2, mITT Population**

| | E50+M[a] | | E25+M[a] | | PBO+M[a] | | Treatment Compared | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | N | Adjusted Mean Change (SE) | Comp. 1 | Comp. 2 | Pairwise p-Value[b] | Adjusted Mean Treatment Difference (95% CI)[b] |
| Week 40 | 196 | 0.41 (0.12) | 198 | 0.46 (0.11) | 192 | 1.28 (0.12) | E50+M | PBO+M | <0.0001 | -0.88 (-1.2, -0.6) |
| | | | | | | | E50+M | E25+M | 0.7427 | -0.05 (-0.4, 0.3) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -0.82 (-1.1, -0.5) |
| Week 48 | 201 | 0.36 (0.12) | 201 | 0.54 (0.12) | 197 | 1.76 (0.13) | E50+M | PBO+M | <0.0001 | -1.40 (-1.7, -1.1) |
| | | | | | | | E50+M | E25+M | 0.3129 | -0.18 (-0.5, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.23 (-1.6, -0.9) |
| Week 56 | 201 | 0.47 (0.13) | 201 | 0.60 (0.13) | 197 | 1.76 (0.13) | E50+M | PBO+M | <0.0001 | -1.29 (-1.6, -0.9) |
| | | | | | | | E50+M | E25+M | 0.4645 | -0.13 (-0.5, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.16 (-1.5, -0.8) |
| Week 64 | 201 | 0.45 (0.13) | 201 | 0.60 (0.13) | 197 | 1.75 (0.13) | E50+M | PBO+M | <0.0001 | -1.30 (-1.7, -0.9) |
| | | | | | | | E50+M | E25+M | 0.3793 | -0.16 (-0.5, 0.2) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.14 (-1.5, -0.8) |
| Week 72 | 201 | 0.33 (0.14) | 201 | 0.67 (0.14) | 197 | 1.93 (0.14) | E50+M | PBO+M | <0.0001 | -1.60 (-2.0, -1.2) |
| | | | | | | | E50+M | E25+M | 0.0816 | -0.34 (-0.7, 0.0) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.26 (-1.6, -0.9) |
| Week 80 | 201 | 0.15 (0.13) | 201 | 0.57 (0.13) | 197 | 1.70 (0.13) | E50+M | PBO+M | <0.0001 | -1.54 (-1.9, -1.2) |
| | | | | | | | E50+M | E25+M | 0.0256 | -0.42 (-0.8, -0.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.13 (-1.5, -0.8) |
| Week 88 | 201 | 0.29 (0.14) | 201 | 0.59 (0.14) | 197 | 1.84 (0.14) | E50+M | PBO+M | <0.0001 | -1.54 (-1.9, -1.2) |
| | | | | | | | E50+M | E25+M | 0.1158 | -0.30 (-0.7, 0.1) |
| | | | | | | | E25+M | PBO+M | <0.0001 | -1.24 (-1.6, -0.9) |

ANCOVA = analysis of covariance; CI = confidence interval; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; LOCF = last observation carried forward; mITT = modified intent to treat; N = total number of subjects; P2 = Period 2; SE = standard error.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. Adjusted mean treatment difference, corresponding 95% CI and F-test (to test whether outcome is independent of treatment) obtained from ANCOVA model: Change = P2 baseline score + treatment + geographic region + DAS28 Strata. DAS28 Strata is defined as DAS28 low disease (≤3.2) or remission (<2.6) at randomization.

Patient Acceptable Symptom State: The proportion of subjects who achieved an acceptable PASS during Period 1 (OC analysis) was 86.80% (Table 35).

**Table 35. Proportions of Subjects Achieving Acceptable PASS during Period 1 in the mITT Population (Observed Cases)**

| | Treatment E50+M[a] n/N [%] (Exact 95% CI) | p-Value* |
|---|---|---|
| Baseline | 370/ 824 [ 44.90] ( 41.47, 48.37) | <0.0001 |
| Week 36 | 697/ 803 [ 86.80] ( 84.26, 89.06) | <0.0001 |

*Tests the null hypothesis that proportion is significantly different from zero using exact binomial test.
CI = confidence interval; E50+M = Etanercept 50 mg + Methotrexate; mITT = modified intent to treat; n = number of subjects achieving acceptable PASS; N = number of subjects assessed at each time point; PASS = patient acceptable symptom state.
a. E50+M = Etanercept 50 mg + Methotrexate.

Statistically significant differences in the proportions of subjects, in Period 2, with an acceptable state in PASS were observed at Week 88 (LOCF) in favor of the E50+M and E25+M treatment groups when compared with the PBO+M group, and also in favor of the E50+M group when compared with the E25+M group (Table 36).

## Table 36. Proportion of Subjects, in Period 2, With an Acceptable State in PASS (LOCF), mITT Population

| | | | | Treatment Compared | | | | |
|---|---|---|---|---|---|---|---|---|
| Week | E50+M[a] n/N (%) | E25+M[a] n/N (%) | PBO+M[a] n/N (%) | Comp. 1 | Comp. 2 | CMH p-Value[b] | Adjusted Odds Ratio[b] (95% CI) | Adjusted Mean Difference in Proportions (%) (95% CI)[c] |
| Week 36 | 188/201 (93.5%) | 178/198 (89.9%) | 185/197 (93.9%) | E50+M | PBO+M | 0.8974 | 1.10 (0.5, 2.5) | -1.21 (-6.3, 3.9) |
| | | | | E50+M | E25+M | 0.1105 | 1.67 (0.8, 3.7) | 2.46 (-3.0, 7.9) |
| | | | | E25+M | PBO+M | 0.1900 | 0.67 (0.3, 1.4) | -3.83 (-11.2, 3.5) |
| Week 64 | 171/190 (90.0%) | 172/194 (88.7%) | 121/184 (65.8%) | E50+M | PBO+M | <0.0001 | 4.18 (2.3, 7.5) | 23.55 (15.5, 31.6) |
| | | | | E50+M | E25+M | 0.4032 | 1.24 (0.6, 2.4) | 1.28 (-4.8, 7.4) |
| | | | | E25+M | PBO+M | <0.0001 | 4.23 (2.4, 7.5) | 21.82 (13.6, 30.0) |
| Week 88 | 178/195 (91.3%) | 166/196 (84.7%) | 131/187 (70.1%) | E50+M | PBO+M | <0.0001 | 3.92 (2.1, 7.2) | 21.10 (12.7, 29.5) |
| | | | | E50+M | E25+M | 0.0272 | 1.90 (1.0, 3.6) | 8.14 (1.0, 15.3) |
| | | | | E25+M | PBO+M | 0.0004 | 2.34 (1.4, 4.0) | 13.03 (4.7, 21.4) |

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; Comp. = comparator; DAS28 = Disease Activity Score in 28 joints; GLM = generalized linear model; LOCF = last observation carried forward; mITT = modified intent to treat; PASS = Patient Acceptable Symptom State.

a. E50+M = Etanercept 50 mg + Methotrexate; E25+M = Etanercept 25 mg + Methotrexate; PBO+M = Placebo + Methotrexate.

b. The adjusted odds ratio compares treatment 1 vs. 2, stratified by DAS28 strata and geographic region. The p-value is from a CMH test of general association, testing treatment effect on response, stratified by DAS28 strata and geographic region.

c. Adjusted Difference in proportion and corresponding 95% CI obtained from GLM model with link = identity, adjusted for geographic region.

**Safety Results:**

Period 1: A summary of the most frequently reported treatment-emergent adverse events (TEAEs) is shown in Table 37. TEAEs were reported in 61.5% of subjects in Period 1. The most frequently reported TEAEs were headache and nasopharyngitis. Among the system organ classes, infections and infestations were the most frequently reported. Treatment related TEAEs were reported by 26.6%% of subjects (Table 38).

**Table 37. Treatment Emergent Adverse Events for Events Having a Frequency of ≥5% (Period 1)**

| System organ Class[a] Preferred Term | E50+M N=834 All Causalities n(%) |
|---|---|
| Any adverse event | 513 (61.5) |
| Infections and infestations | 279 (33.5) |
| Nasopharyngitis | 45 (5.4) |
| Nervous system disorders | 84 (10.1) |
| Headache | 51 (6.1) |

AEs and SAEs are not separated out in this table.
Classifications of AEs are based on the MedDRA.
AEs = adverse events; E50+M = Etanercept 50 mg + Methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; SAEs = serious adverse events.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

**Table 38. Treatment Emergent Treatment Related Adverse Events for Events Having a Frequency of ≥2% (Period 1)**

| System organ Class[a] Preferred Term | Treatment Related |
|---|---|
| Any adverse event | 222 (26.6) |
| Gastrointestinal disorders | 35 (4.2) |
| Nausea | 21 (2.5) |
| General disorders and administration site conditions | 63 (7.6) |
| Injection site erythema | 23 (2.8) |
| Injection site reaction | 20 (2.4) |
| Infections and infestations | 135 (16.2) |
| Bronchitis | 17 (2.0) |
| Nasopharyngitis | 18 (2.2) |
| Upper respiratory tract infection | 17 (2.0) |

AEs and SAEs are not separated out in this table.
Classifications of AEs are based on the MedDRA.
AEs = adverse events; E50+M = Etanercept 50 mg + Methotrexate; MedDRA = Medical Dictionary for Regulatory Activities; SAEs = serious adverse events.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report 2 or more different AEs within the higher level category.

Treatment-emergent SAEs occurred in 4.6% of subjects. The most frequently reported treatment-emergent SAEs were pneumonia, reported by 5 subjects (0.6%), and cellulitis, acute pyelonephritis, and basal cell carcinoma, reported in 2 subjects each (Table 39).

## Table 39. Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Events (Period 1)

| System Organ Class[a]<br>Preferred Term | E50+M[b]<br>n=834 |
|---|---|
| Any Adverse Event | 38 (4.6) |
| Blood and lymphatic system disorders | 1 (0.1) |
| Anaemia | 1 (0.1) |
| Cardiac disorders | 2 (0.2) |
| Atrial fibrillation | 1 (0.1) |
| Myocardial infarction | 1 (0.1) |
| Gastrointestinal disorders | 2 (0.2) |
| Gastrointestinal haemorrhage | 1 (0.1) |
| Rectal haemorrhage | 1 (0.1) |
| General disorders and administration site conditions | 1 (0.1) |
| Pyrexia | 1 (0.1) |
| Infections and infestations | 14 (1.7) |
| Arthritis bacterial | 1 (0.1) |
| Bronchopneumonia | 1 (0.1) |
| Cellulitis | 2 (0.2) |
| Cystitis | 1 (0.1) |
| H1N1 influenza | 1 (0.1) |
| Pneumonia | 5 (0.6) |
| Pyelonephritis acute | 2 (0.2) |
| Tooth abscess | 1 (0.1) |
| Injury, poisoning and procedural complications | 6 (0.7) |
| Accidental overdose | 1 (0.1) |
| Facial bones fracture | 1 (0.1) |
| Foreign body | 1 (0.1) |
| Joint sprain | 1 (0.1) |
| Tibia fracture | 1 (0.1) |
| Upper limb fracture | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 3 (0.4) |
| Bursitis | 1 (0.1) |
| Chondropathy | 1 (0.1) |
| Osteonecrosis | 1 (0.1) |
| Neoplasms benign, malignant and unspecified (inclusive cysts and polyps) | 5 (0.6) |
| Basal cell carcinoma | 2 (0.2) |
| Cervicitis human papilloma virus | 1 (0.1) |
| Colon cancer | 1 (0.1) |
| Uterine leiomyoma | 1 (0.1) |
| Nervous system disorders | 2 (0.2) |
| Carotid artery stenosis | 1 (0.1) |
| Headache | 1 (0.1) |
| Transient ischaemic attack | 1 (0.1) |
| Psychiatric disorders | 1 (0.1) |
| Depression | 1 (0.1) |
| Renal and urinary disorders | 2 (0.2) |
| Calculus urinary | 1 (0.1) |
| Renal failure acute | 1 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 3 (0.4) |
| Asthma | 1 (0.1) |
| Chronic obstructive pulmonary disease | 1 (0.1) |
| Pneumonitis | 1 (0.1) |

**Table 39. Number (%) of Subjects Reporting Treatment Emergent Serious Adverse Events (Period 1)**

| System Organ Class[a]<br>Preferred Term | E50+M[b]<br>n=834 |
|---|---|
| Skin and subcutaneous tissue disorders | 1 (0.1) |
| Skin ulcer | 1 (0.1) |
| Vascular disorders | 1 (0.1) |
| Deep vein thrombosis | 1 (0.1) |

Classifications of adverse events are based on the MedDRA.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report two or more different AEs within the higher level category.
b. Etanercept 50 mg + Methotrexate.

Twenty-two (22, 2.6%) subjects discontinued from the study because of TEAEs (Table 40). The only event leading to withdrawal in more than 1 subject was pneumonia, which lead to discontinuation for 3 subjects, 2 of whom died.

**Table 40. Number (%) of Subjects Reporting Treatment Emergent Adverse Events Causing Withdrawal (Period 1)**

| System Organ Class[a]<br>Preferred Term | E50+M[b]<br>n=834 |
|---|---|
| Any Adverse Event | 22 (2.6) |
| Blood and lymphatic system disorders | 1 (0.1) |
| Leukopenia | 1 (0.1) |
| Lymphopenia | 1 (0.1) |
| Gastrointestinal disorders | 1 (0.1) |
| Nausea | 1 (0.1) |
| Hepatobiliary disorders | 1 (0.1) |
| Cytolytic hepatitis | 1 (0.1) |
| Infections and infestations | 9 (1.1) |
| Arthritis bacterial | 1 (0.1) |
| Bronchopneumonia | 1 (0.1) |
| Cellulitis | 1 (0.1) |
| Furuncle | 1 (0.1) |
| Pertussis | 1 (0.1) |
| Pneumonia | 3 (0.4) |
| Pyelonephritis acute | 1 (0.1) |
| Injury, poisoning and procedural complications | 1 (0.1) |
| Drug exposure during pregnancy | 1 (0.1) |
| Neoplasms benign, malignant and unspecified (inclusive cysts and polyps) | 2 (0.2) |
| Cervicitis human papilloma virus | 1 (0.1) |
| Colon cancer | 1 (0.1) |
| Nervous system disorders | 2 (0.2) |
| Dysgeusia | 1 (0.1) |
| Headache | 1 (0.1) |
| Psychiatric disorders | 1 (0.1) |
| Depression | 1 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 3 (0.4) |
| Asthma | 1 (0.1) |
| Lower respiratory tract inflammation | 1 (0.1) |
| Pneumonitis | 1 (0.1) |
| Skin and subcutaneous tissue disorders | 4 (0.5) |
| Dermal cyst | 1 (0.1) |
| Rash | 1 (0.1) |
| Skin ulcer | 1 (0.1) |
| Urticaria | 1 (0.1) |

Classifications of adverse events are based on the MedDRA.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may report two or more different AEs within the higher level category
b. Etanercept 50 mg + Methotrexate.

Deaths: During period 1 of the study, 2 subjects in Mexico died of pneumonia judged related to the study drug during the 2009 H1N1 influenza outbreak.

Period 2: A total of 351 subjects (58.1%) reported TEAEs. The numbers of subjects with at least 1 TEAE were as follows: 124 subjects (61.4%) in the E50+M group; 122 subjects in the E25+M group (60.4%); 105 subjects (52.5%) in the PBO+M group. TEAEs in the system organ class of infections and infestations were the most commonly reported, occurring in

72 subjects in the E50+M group, 60 subjects in the E25+M group and 67 subjects in the PBO+M group. Non-serious TEAEs reported by ≥5% of subjects in Period 2 are presented in Table 41.

**Table 41. Treatment Emergent Non-Serious Adverse Events for Events Having a Frequency of ≥5% (Period 2)**

| System Organ Class[a] Preferred Term | Overall p-Value | E50+M N=202 n (%) | E25+M N=202 n (%) | PBO+M N=200 n (%) | Total N=604 n (%) |
|---|---|---|---|---|---|
| Any AEs | 0.389 | 32 (15.8) | 23 (11.4) | 25 (12.5) | 80 (13.2) |
| Infections and infestations | 0.389 | 32 (15.8) | 23 (11.4) | 25 (12.5) | 80 (13.2) |
| Bronchitis | 0.337 | 12 (5.9) | 11 (5.4) | 6 (3.0) | 29 (4.8) |
| Nasopharyngitis | 0.171 | 18 (8.9) | 10 (5.0) | 10 (5.0) | 38 (6.3) |
| Pharyngitis | 0.056 | 3 (1.5) | 5 (2.5) | 11 (5.5) | 19 (3.1) |

Classifications of adverse events are based on the MedDRA.
Overall p-value: refers to number of subjects data. p-Value for Chi-Square.
AE = adverse events; E25+M = Etanercept 25 mg + Methotrexate;
E50+M = Etanercep 50 mg + methotrexate; MedDRA = Medical Dictionary for Regulatory Activities;
PBO+M = Placebo + Methotrexate.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

Overall there were 7 subjects who had severe, related TEAEs (4 cases in 4 subjects in the E50+M group, 5 cases in 2 subjects in the E25+M group, and 2 cases in 1 subject in the PBO+M group). A total of 2 subjects had life-threatening TEAEs (1 subject in the E50+M group and 1 subject in the PBO+M group), neither of which were considered by the Investigator to be related to study treatment.

In the E50+M group, the severe, related TEAEs consisted of polyp colorectal, rhinitis, upper respiratory tract infection, and dermal cyst, in 1 subject each. In the E25+M group, the severe, related TEAEs consisted of acute myocardial infarction in 1 subject and bladder cancer, bladder neoplasm, hematuria, and urinary bladder polyp in another subject. In the PBO+M group, the severe, related TEAEs consisted of sepsis and urinary tract infection in 1 subject.

The life-threatening TEAEs consisted of sepsis and pulmonary embolism in the E50+M group (1 subject each) and pyloric ulcer in the PBO+M group.

A total of 115 subjects (19.0%) had treatment-related TEAEs that were considered by the Investigator to be related to study treatment (Table 42).

**Table 42. Treatment-Related Adverse Events for Events Having a Frequency of ≥2% (Period 2)**

| System Organ Class[a] Preferred Term | E50+M n=202 | E25+M n=202 | PBO+M n=200 | Total n=604 |
|---|---|---|---|---|
| Any related AE | 37 (18.3) | 42 (20.8) | 36 (18.0) | 115 (19.0) |
| Gastrointestinal disorders | 8 (4.0) | 5 (2.5) | 2 (1.0) | 15 (2.5) |
| Nausea | 4 (2.0) | 2 (1.0) | 3 (1.5) | 9 (1.5) |
| Infections and infestations | 27 (13.4) | 29 (14.4) | 28 (14.0) | 84 (13.9) |
| Bronchitis | 4 (2.0) | 4 (2.0) | 3 (1.5) | 11 (1.8) |
| Nasopharyngitis | 2 (1.0) | 3 (1.5) | 5 (2.5) | 10 (1.7) |
| Pharyngitis | 3 (1.5) | 5 (2.5) | 7 (3.5) | 15 (2.5) |
| Respiratory tract infection | 1 (0.5) | 5 (2.5) | 1 (0.5) | 7 (1.2) |
| Sinusitis | 1 (0.5) | 1 (0.5) | 4 (2.0) | 6 (1.0) |
| Upper respiratory tract infection | 4 (2.0) | 4 (2.0) | 5 (2.5) | 13 (2.2) |
| Investigations | 4 (2.0) | 6 (3.0) | 7 (3.5) | 17 (2.8) |
| Alanine aminotransferase increased | 1 (0.5) | 3 (1.5) | 5 (2.5) | 9 (1.5) |

Classifications of adverse events are based on the MedDRA.
Overall p-value: refers to number of subjects data. p-Value for Chi-Square.
AE = adverse events; E25+M = Etanercept 25 mg + Methotrexate;
E50+M = Etanercept 50 mg + methotrexate; MedDRA = Medical Dictionary for Regulatory Activities;
PBO+M = Placebo + Methotrexate.
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

A total of 35 subjects (5.8%) reported at least 1 SAE (Table 44). Thirteen of these subjects were in the E50+M group, 7 subjects were in the E25+M group, and 15 subjects were in the PBO+M group. No specific SAE was reported in more than 2 subjects and there were no statistically significant differences among the treatment groups.

## Table 43. Number (%) of Subjects Reporting Serious Adverse Events (Period 2)

| System Organ Class[a]<br>MedDRA Preferred Term | Overall p-Value | E50+M N=202 n (%) | E25+M N=202 n (%) | PBO+M N=200 n (%) | Total N=604 n (%) |
|---|---|---|---|---|---|
| Any serious adverse event | 0.199 | 13 (6.4) | 7 (3.5) | 15 (7.5) | 35 (5.8) |
| Cardiac disorders | 1.000 | 1 (0.5) | 1 (0.5) | 1 (0.5) | 3 (0.5) |
| Acute myocardial infarction | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Angina pectoris | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Myocardial infarction | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Eye disorders | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Refraction disorder | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Gastrointestinal disorders | 0.168 | 1 (0.5) | 0 | 3 (1.5) | 4 (0.7) |
| Gastric ulcer | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Gastritis | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Polyp colorectal | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Umbilical hernia | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| General disorders and administration site conditions | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Oedema peripheral | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Hepatobiliary disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Cholecystitis | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Immune system disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Sarcoidosis | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Infections and infestations | 0.218 | 3 (1.5) | 0 | 3 (1.5) | 6 (1.0) |
| Bronchitis | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Gastroenteritis | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| H1N1 influenza | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Sepsis | 0.604 | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Upper respiratory tract infection | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Urinary tract infection | 0.132 | 0 | 0 | 2 (1.0) | 2 (0.3) |
| Injury, poisoning and procedural complications | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Overdose | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Metabolism and nutrition disorders | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Dehydration | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 0.439 | 1 (0.5) | 1 (0.5) | 3 (1.5) | 5 (0.8) |
| Arthralgia | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Intervertebral disc protrusion | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Muscular weakness | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Osteonecrosis | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Rheumatoid arthritis | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 0.418 | 3 (1.5) | 4 (2.0) | 1 (0.5) | 8 (1.3) |
| Basal cell carcinoma | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Bladder cancer | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Bladder neoplasm | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Malignant melanoma | 0.604 | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Malignant melanoma in situ | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Ovarian adenoma | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Prostate cancer | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Squamous cell carcinoma of skin | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Thyroid cancer | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |

**Table 43. Number (%) of Subjects Reporting Serious Adverse Events (Period 2)**

| System Organ Class[a]<br>MedDRA Preferred Term | Overall p-Value | E50+M N=202 n (%) | E25+M N=202 n (%) | PBO+M N=200 n (%) | Total N=604 n (%) |
|---|---|---|---|---|---|
| Nervous system disorders | 0.362 | 0 | 1 (0.5) | 2 (1.0) | 3 (0.5) |
| Cerebral infarction | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Cerebrovascular accident | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Convulsion | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Pregnancy, puerperium and perinatal conditions | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Pregnancy | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Psychiatric disorders | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Depression | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Renal and urinary disorders | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Haematuria | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Urinary bladder polyp | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Reproductive system and breast disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Endometrial hyperplasia | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Respiratory, thoracic and mediastinal disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Pulmonary embolism | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Skin and subcutaneous tissue disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Skin ulcer | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Vascular disorders | 0.132 | 0 | 0 | 2 (1.0) | 2 (0.3) |
| Thrombophlebitis | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Venous thrombosis | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |

Overall p-value: refers to "Number of Subjects" data. p-Value for Chi-Square.
E25+M = Etanercept 25 mg + Methotrexate; E50+M = Etanercept 50 mg + Methotrexate;
MedDRA = Medical Dictionary for Regulatory Activities; PBO+M = Placebo + Methotrexate.

a. Totals for the "Number of Subjects" at a higher level are not necessarily the sum of those at the lower levels, since a subject may report 2 or more different adverse events within the higher level category.

Discontinuations: Sixteen subjects (2.6%) were withdrawn from the study in Period 2 due to TEAEs (Table 44). Seven of these subjects were in the E50+M group, 4 subjects were in the E25+M group, and 5 subjects were in the PBO+M group. There were no statistically significant differences among the treatment groups.

**Table 44. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events Causing Withdrawal (Period 2)**

| System Organ Class[a]<br>MedDRA Preferred Term | Overall p-Value | E50+M N=202 n (%) | E25+M N=202 n (%) | PBO+M N=200 n (%) | Total N=604 n (%) |
|---|---|---|---|---|---|
| Any adverse events | 0.641 | 7 (3.5) | 4 (2.0) | 5 (2.5) | 16 (2.6) |
| Blood and lymphatic system disorders | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Leukopenia | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| General disorders and administration site conditions | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Oedema peripheral | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Infections and infestations | 0.604 | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Sepsis | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Upper respiratory tract infection | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Urinary tract infection | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Investigations | 0.136 | 0 | 2 (1.0) | 0 | 2 (0.3) |
| Alanine aminotransferase increased | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Aspartate aminotransferase increased | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| White blood cell count decreased | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Metabolism and nutrition disorders | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Diabetes mellitus | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Musculoskeletal and connective tissue disorders | 0.604 | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Muscular weakness | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Rheumatoid arthritis | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 0.822 | 2 (1.0) | 2 (1.0) | 1 (0.5) | 5 (0.8) |
| Bladder cancer | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Bladder neoplasm | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Malignant melanoma | 0.604 | 1 (0.5) | 0 | 1 (0.5) | 2 (0.3) |
| Malignant melanoma in situ | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Thyroid cancer | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Pregnancy, puerperium and perinatal conditions | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Pregnancy | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Renal and urinary disorders | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Haematuria | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Urinary bladder polyp | 0.369 | 0 | 1 (0.5) | 0 | 1 (0.2) |
| Skin and subcutaneous tissue disorders | 0.367 | 2 (1.0) | 0 | 1 (0.5) | 3 (0.5) |
| Alopecia areata | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Dermal cyst | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Skin ulcer | 0.369 | 1 (0.5) | 0 | 0 | 1 (0.2) |
| Vascular disorders | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |
| Hypertension | 0.364 | 0 | 0 | 1 (0.5) | 1 (0.2) |

E25+M = Etanercept 25 mg + Methotrexate; E50+M = Etanercept 50 mg + Methotrexate;
MedDRA = Medical Dictionary for Regulatory Activities; PBO+M = Placebo + Methotrexate.
Overall p-value: refers to "Number of Subjects" data. p-Value for Chi-Square.

a. Totals for the "Number of Subjects" at a higher level are not necessarily the sum of those at the lower levels, since a subject may report 2 or more different adverse events within the higher level category.

Deaths: There were 2 deaths during Period 2, both of which occurred in the E50+M group and both of which were unrelated to study treatment. One subject died from suspected pulmonary embolism and one subject died from septicemia (sepsis).

**CONCLUSION:**

Period 1: In this population of male and female subjects with moderate RA, the combination of etanercept and MTX was efficacious with clinically meaningful improvements in change from Baseline in DAS28, prorated swollen and painful joint counts, physician and patient global assessments, morning stiffness, general health and pain VAS, CDAI, SDAI, ESR and CRP. A substantial number of subjects achieved DAS28 low disease activity and remission, ACR20, ACR50, ACR70, and EULAR responses. The study treatment was well tolerated, and there were no new safety signals.

Period 2: The primary objective of this study was met. The percent of subjects maintaining DAS28 low disease activity at Week 88 was significantly higher in the E50+M (82.6%) and E25+M (79.1%) treatment groups compared with the PBO+M group (42.6%); $p<0.0001$ vs either etanercept group. Except for ACR 90 response at Week 40, both etanercept combination treatment groups demonstrated statistically significant differences compared with PBO+M across all secondary efficacy endpoints at every post-randomization time point during Period 2. There were also statistically significant differences in the change from Period 2 baseline in adjusted mean DAS28 scores favouring both etanercept combination treatment groups compared with PBO+M at every time point during Period 2. There were no new safety signals.