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

PROTOCOL NO.: 0881X1-4524 (B1801020)

PROTOCOL TITLE: A 3-Phase Study to Evaluate Sustained Remission and Productivity Outcomes in Subjects With Early Rheumatoid Arthritis Initiated on Treatment With Etanercept Plus Methotrexate

Study Centers: In Part 1, a total of 57 centers took part in the study and randomized subjects: 7 in France, 11 in Germany, 1 in Ireland, 2 in Italy, 1 in Monaco, 3 in the Netherlands, 8 in Poland, 1 in Qatar, 6 in Romania, 1 in the Russian Federation, 6 in Spain, , 3 in Switzerland, 7 in the United Kingdom.

In Part 2, a total of 50 centers took part in the study and randomized subjects: 6 in France, 8 in Germany, 1 in Ireland, 2 in Italy, 1 in Monaco, 2 in the Netherlands, 8 in Poland, 1 in Qatar, 5 in Romania, 1 in the Russian Federation, 6 in Spain, 3 in Switzerland, and 6 in the United Kingdom.

In Part 3, a total of 58 centers took part in the study and randomized subjects: 7 in France, 11 in Germany, 1 in Ireland, 3 in Italy, 1 in Monaco, 3 in the Netherlands, 8 in Poland, 1 in Qatar, 6 in Romania, 1 in the Russian Federation, 6 in Spain, 3 in Switzerland, and 7 in the United Kingdom.

Study Initiation and Final Completion Dates: Part 1: 20 October 2009 to 13 October 2011, Part 2: 11 November 2010 to 19 June 2012, and Part 3: 20 October 2009 to 17 December 2012 respectively.

Phase of Development: Phase 4

Study Objectives:

Primary Objective: Part 1, 2, and 3

For the Part 1 responders, to assess the efficacy of etanercept (ETN) 25 mg once weekly, in combination with Methotrexate ([MTX] +ETN [E25] for the maintenance of sustained remission for a further 39-week period in Part 2, in comparison with continued placebo.

The hypothesis of primary interest was the superiority of E25 + MTX compared with placebo Part 1, 2, and 3, based on the proportion of subjects with sustained remission at Week 91.

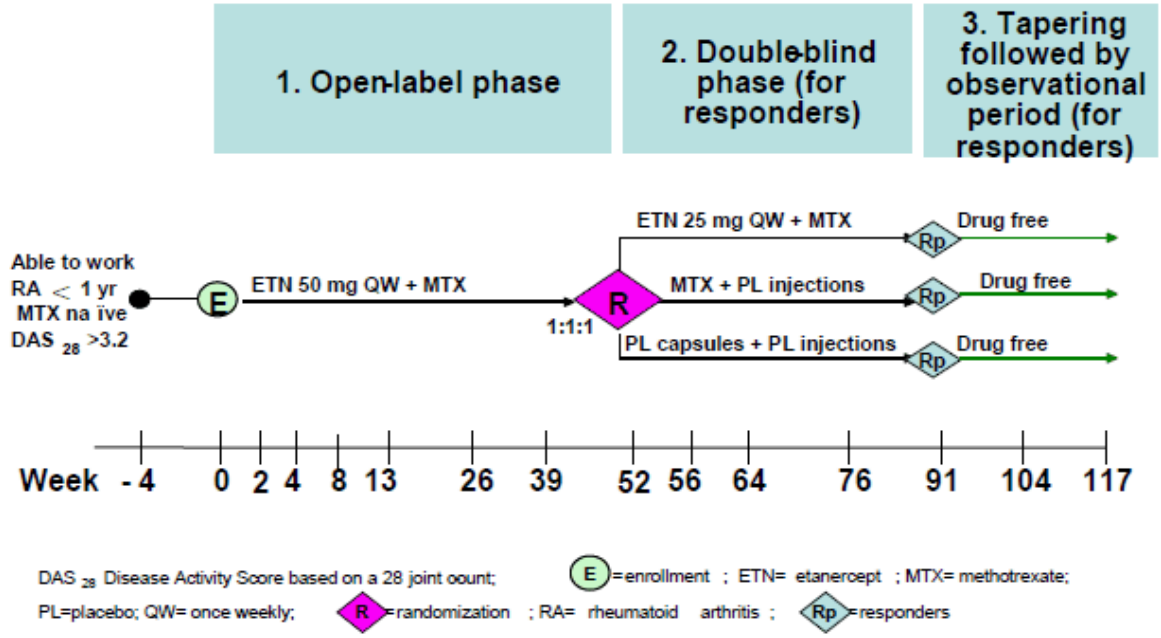
Secondary Objectives: Parts 1, 2, and 3

- To assess productivity, as measured by the Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis (WPAI: RA). WPAI: RA was measured approximately every 13 weeks and the total productivity impact for each subject across all visits was evaluated.
- To evaluate other clinical efficacy endpoints.
- To assess the safety of the treatment regimens over the 3 study parts.

METHODS

Study Design: This was a Phase 4, 121-week, prospective, 3-part (Part 1, 2, and 3), parallel-group, multicenter, outpatient study that is ongoing (Figure 1). The study is also known as the PRIZE (Productivty and Remission in a randomized controlled trial of ETN versus standard of care in Early rheumatoid arthritis) study.

Figure 1. Overview of the Study Design



The overall duration of subject participation in this study was a maximum of approximately 121 weeks, including screening (up to 4 weeks period), Part 1 (52-week open-label period), Part 2 (39-week double-blind randomized period), Part 3 (26-week tapering period), and a 4-week drug-free observational period. Subjects withdrawn from the study were not replaced, regardless of the reason for withdrawal.

Part 1: This was a 52-week, open-label, single-arm period in which all subjects were treated with ETN 50 mg (E50) plus MTX (starting dose of 10 mg) once weekly. Optimization of medication in the form of a corticosteroid boost was to be used in all subjects not achieving

low disease activity, ie, a Disease Activity Score (DAS) based on a 28-joint count (DAS28) >3.2 at Week 13 and/or Week 26.

Subjects who were not in sustained remission or who did not have low disease activity (defined as DAS28 ≤3.2) at the Week 39 visit were classified as Part 1 non-responders and withdrawn from the study. At Week 52, subjects were defined as Part 1 responders or Part 1 non-responders. Part 1 responders were defined as subjects with DAS28 ≤3.2 at Week 39 and DAS28 <2.6 at Week 52. Part 1 non-responders to ETN plus MTX treatment were withdrawn from the study and completed all procedures at the Early Discontinuation (ED) visit, which included a safety follow-up telephone call at approximately 28 days after ED or last dose of study drug.

Part 2: This was a 39-week, double-blind, randomized, placebo-controlled, 3-arm comparison of dose reduction or withdrawal from treatment with study drugs (E50+MTX) in subjects who achieved response during Part 1, which were randomized (1:1:1 ratio) to receive E25+MTX, etanercept placebo injection plus MTX capsules (E-PBO+MTX), or or etanercept placebo injection plus MTX placebo capsules (E-PBO+M-PBO). Tapering down from study drugs etanercept ETN and MTX: for subjects randomized to E-PBO+MTX or E-PBO+M-PBO, E50 was tapered down during the first 2 weeks of double-blind treatment: from E50 to E25 in the first week and from 25 mg to PBO in the second week. For subjects randomized to PBO+PBO, an additional 2-to 4-week period of double-blind MTX tapering (depending on the optimized MTX dose), followed the first week of ETN dose-tapering.

Subjects with DAS28>3.2 at visits Week 56 or Week 64 will be given a boost of corticosteroids. If DAS28>3.2 at the subsequent visit, subjects will be defined as Part 2 non-responders, withdrawn from the study and treated entirely at the discretion of the Investigator. At Week 91, subjects in all 3 arms were defined as Part 2 responders or Part 2 nonresponders. Responders are defined as subjects in sustained remission (DAS28<2.6) or with low disease activity (2.6≤ DAS28≤3.2) at the Week 91 visit. Part 2 non-responders were withdrawn from the study and completed all procedures at the ED visit, which included a safety follow-up telephone call at approximately 28 days after ED or last dose of study drug.

Part 3: This was a 26-week observational period in which Part 2 responders or with low disease activity progressively stopped treatment at Week 91 visit. It included a 2 to 4-week period of double-blind MTX tapering (depending on the optimized MTX dose), followed by an observational period until Week 117.. Subjects who completed the full study or discontinue more than 28 days after the last dose of test article would not have a follow-up telephone call.

A flowchart of the study procedures for Part 1, Part 2, and Part 3 of the study is presented in Table 1.

Table 1. Schedule of Study Procedures and Evaluations for Parts 1, 2, and 3

Study Weeks[a]	**Weeks -4 to 0**	**Week 0**	**Week 2**	**Weeks 4, 8**	**Weeks 13,26,39**[b]	**Week 52**[b]	**Week 56**	**Weeks 64, 76**[b]	**Week 91**[b]	**Weeks 104, 117**	**ED**[c]
Study Part	**Screening**[d]	**Baseline**	**Part 1**				**Part 2**			**Part 3**	
	Visit 1	**Visit 2**	**Visit 3**	**Visits 4, 5**	**Visits 6 to 8**	**Visit 9**	**Visit 10**	**Visits 11, 12**	**Visit 13**	**Visits 14, 15**	**Visit 99**[e]
Informed consent	X										
Inclusion/exclusion	X	X									
Part 1 enrollment		X									
Part 2 randomization						X					
Response assessment					X (Visit 8 only)[b]	X[b]		X[b]	X[b]		
Demographics	X										
Medical RA history	X										
Cardiovascular diagnosis and family history	X										
Substance usage	X									X (Visit 15 only)	X
Pregnancy test[f]	X	X								X (Visit 15 only)	X
Physical examination	X				X (Visit 7 only)	X		X (Visit 12 only)	X	X (Visit 15 only)	X
Vital signs[g]	X	X[h]	X	X	X	X	X	X	X	X	X
ESR[i]	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry, hematology, urinalysis, hs-CRP	X	X[h]	X	X (Visit 5 only)	X	X		X	X	X	X
Rheumatoid factor and anti-cyclic citrullinated peptide	X										

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Study Part	**Screening**[d]	**Baseline**	**Part 1**				**Part 2**			**Part 3**	
	Visit 1	**Visit 2**	**Visit 3**	**Visits 4, 5**	**Visits 6 to 8**	**Visit 9**	**Visit 10**	**Visits 11, 12**	**Visit 13**	**Visits 14, 15**	**Visit 99**[e]
Fasting metabolic biomarkers/ cardiovascular labs/ urine chemistry[j]		X			X (Visit 6 only)						X[k]
Fasting reminder call[l]		X			X (Visit 6 only)						X[k]
Chest radiography/ TB test[m]	X										
Hand, wrist, and foot radiographs[n]		X				X			X		X[n]
RA-WIS		X			X	X		X	X	X	X
VOLP		X			X	X		X	X	X	X
WPAI: RA		X			X	X		X	X	X	X
VAS assessments: Subject pain Subject global Subject general health Physician global	X	X	X	X	X	X	X	X	X	X	X
DAS28/44 joint assessment[o]	X	X	X	X	X[p,q]	X	X[r]	X[r]	X	X	X
HAQ		X	X	X	X	X	X	X	X	X	X
Quality of life tools: SF-36 EQ-5D		X	X	X	X	X	X	X	X	X	X
PASS		X	X	X	X	X	X	X	X	X	X
FACIT		X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications[s]	X	X	X	X	X	X	X	X	X	X	X

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Study Part	**Screening**[d]	**Baseline**	**Part 1**				**Part 2**			**Part 3**	
	Visit 1	**Visit 2**	**Visit 3**	**Visits 4, 5**	**Visits 6 to 8**	**Visit 9**	**Visit 10**	**Visits 11, 12**	**Visit 13**	**Visits 14, 15**	**Visit 99**[e]
Dispense/review subject diary card		X	X	X	X	X[t]	X	X	X[t]	X	X[u]
Dispense investigational product and folic acid		X[v]	X	X	X	X[t]	X	X	X[t]		
Return investigational product/drug accountability			X	X	X	X	X	X	X	X (Visit 14 only)	X[u]
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Sample banking for exploratory research[w]		X			X (Visit 6, 7 only)	X		X (Visit 12 only)	X	X (Visit 15 only)	X

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DAS28/44 = Disease Activity Score (based on a 28- or 44-joint count); ED = early discontinuation; eCRF = electronic case report form; EQ-5D = EuroQol-5 Dimensions; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; hs-CRP = high sensitivity C-reactive protein; IVRS = interactive voice response system; MTX = methotrexate; PASS = Patient Acceptable Symptom State; PPD = purified protein derivative; RA = rheumatoid arthritis; RA-WIS = Rheumatoid Arthritis Work Instability Scale; SAE = serious adverse event; SF-36 = Short Form 36-item Health Survey; TB = tuberculosis; TNF = tumor necrosis factor; ULN = upper limit of normal; VAS = visual analog scale; VOLP = Valuation of Lost Productivity Questionnaire; WPAI: RA = Work Productivity and Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Visit window: The visit window for Visits 2 through 8, 10 through 12, and Visits 14 and 15 was ±4 days. Visit 9 (Week 52) was to occur 12 months ±2 weeks after the Baseline visit (Week 0). Visit 13 (Week 91) should have been occurred 9 months ±2 weeks after Visit 9 (Week 52).
b. Non-responders at Week 39, Week 52, Week 64, Week 76, and Week 91 were to be withdrawn from the study and were to complete all procedures at the ED visit.
c. A follow-up phone call was to be performed approximately 28 days after the early discontinuation visit to assess any AEs/SAEs since the previous study visit. Subjects who completed the full study or discontinued more than 28 days after the last dose of test article would not have a follow-up telephone call.
d. Screening visit procedures (Visit 1) were to preferably all occur 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 to be a minimum of 4 days but no more than 4 weeks and was only to be extended to 6 weeks when TB prophylactic treatment was necessary. Results of all screening procedures were to be available at the Baseline visit (Visit 2) to determine eligibility.
e. All subjects who discontinued early, including non-responders, were to be withdrawn from the study and treated entirely at the discretion of the Investigator.

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Study Part	Screening[d]	Baseline	Part 1				Part 2			Part 3	
	Visit 1	Visit 2	Visit 3	Visits 4, 5	Visits 6 to 8	Visit 9	Visit 10	Visits 11, 12	Visit 13	Visits 14, 15	Visit 99[e]

f. For women of childbearing potential only (serum test at screening, urine test at baseline before investigational product administration, or at ED or Week 117). Pregnancy testing could have been repeated during the study at the discretion of the Investigator.
g. Included sitting blood pressure and pulse rate at all visits; weight at Visit 2, 6, 7, 8, 9, 11, 12, 13, 14, 15 and ED; hip circumference, and waist circumference at Visit 1, 9, 13 and ED; and height at Visit 1.
h. Vital signs and noted labs did not have to be repeated at the Baseline visit if completed at the Screening visit ≤14 days from Baseline visit.
i. The ESR was to be determined at the investigative site using an ESR kit supplied by the centralized laboratory. Baseline ESR was to be assessed prior to eligibility determination. ESR was completed on the same day as all scheduled visits, when the ESR blood sample was not drawn or the test was unable to complete, the blood sample was drawn within +4 days of the scheduled visit to complete the DAS28 calculation for the visit.
j. All fasting lab tests were to be collected at the subject's scheduled visit; however, to accommodate rare instances when a subject was unable to fast (or did not fast), fasting lab samples could have been drawn within 4 days of the visit.
k. Metabolic biomarkers/cardiovascular labs/urine chemistry were to be completed for ED subjects who withdrew prior to Week 13.
l. Fasting reminder phone call was to occur at least 1 day before the Baseline Visit and Visit 6, or the ED Visit, as applicable.
m. A chest radiograph was performed at the Screening visit (Visit 1) only and read locally by a qualified reader. A chest radiograph was not required if it had been done within the past 12 months of screening and the report was available and included in 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 such as PPD. If the subject was known to be PPD positive, the test need not be repeated if documentation was available to show the subject met local criteria for anti-TNF therapy and had not had TB in the last 2 years. If the subject had a documented negative PPD test within 3 months prior to the Screening visit, the test need not be repeated. If subject received chemoprophylaxis during the screening period, blood samples for ALT and AST were to be drawn between 3 and 4 weeks after initiating chemoprophylaxis and at least 4 days prior to the planned Baseline visit to confirm that ALT and AST were not exclusionary (>2 times ULN).
n. Radiographs were assessed by a central blind assessor. Radiographs were to be completed upon ED only if the withdrawal visit was during Part 1 and was 4 months or more after the previous radiographic assessment.
o. It was recommended that the same qualified personnel complete these assessments at each visit.
p. Subjects with DAS28 >3.2 at the Week 13 Visit and/or at the Week 26 visit were to be given a corticosteroid boost. Subjects who were not in remission or with low disease activity at the Week 39 Visit were to be classified as a Part 1 non-responder, withdrawn from the study, and treated entirely at the discretion of the Investigator. It was also performed for Part 2, Visits 10 to 15.
q. If DAS28 criteria were met at the Week-39 Visit, confirm the MTX dose in IVRS for potential Part 2 participation.
r. Subjects with DAS28>3.2 at the Week 56 visit OR at the Week 64 visit will be given a corticosteroid boost. At the subsequent visit, if DAS28>3.2, subjects will be classified as a Part 2 non-responder, withdrawn from the study and treated entirely at the discretion of the Investigator.
s. Nonpharmacologic treatments and/or therapies and concomitant medications received after the date of first administration of investigational product and

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Study Part	Screening[d]	Baseline	Part 1				Part 2			Part 3	
	Visit 1	Visit 2	Visit 3	Visits 4, 5	Visits 6 to 8	Visit 9	Visit 10	Visits 11, 12	Visit 13	Visits 14, 15	Visit 99[e]

until Week 117 or the Early Discontinuation visit were to be recorded on the eCRF.

t. The MTX treatment was tapered by 5 mg weekly in a double-blind manner at Week 52 (Visit 9) for subjects randomized to placebo MTX and at Week 91 (Visit 13) for all other subjects.

u. Review subject diary card and drug accountability (for subjects who withdrew prior to Week 52).

v. The first dose was to be administered in the Investigator's site office by study personnel after all baseline evaluations were completed.

w. The molecular profiling (pharmacogenomic) research component was performed only at participating sites.

Number of Subjects (Planned and Analyzed): In Part 1, 300 subjects were planned, an overall 356 subjects were screened (including 5 in Qatar, 17 in Spain, 3 in Italy, 77 in Germany, 84 in Poland, 24 in Romania, 16 in Switzerland, 4 in Ireland, 15 in the Netherlands, 5 in Monaco, 4 in Russian Federation, 83 in the United Kingdom, and 29 in France), and 306 subjects received at least 1 dose of study drug in Part 1. Of these 306 subjects, 1 subject did not meet response criteria and thus was erroneously randomized to Part 2. All treated subjects were analyzed for efficacy and safety. A total of 193 subjects (ie, responders in Part 1) continued treatment in Part 2, and a total of 131 subjects continued the study in Part 3.

Diagnosis and Main Criteria for Inclusion:

Part 1:

MTX-naïve male and nonpregant female subjects 18 years or older with a diagnosis of rheumatoid arthritis (RA) with functional status of Class I, II, or III as defined by the 1987 American College of Rheumatology (ACR) Revised Criteria, active disease at time of enrollment (ie, DAS28 >3.2), with symptom (swollen joints) onset ≤12 months prior to enrollment. Subjects were in paid employment, either full or part time, or were in unpaid but measurable work, such as caring for a family and home. Exclusionary criteria included subjects who had received any previous treatment with MTX, or any previous treatment with ETN or other tumor necrosis factor (TNF) antagonist (eg, a TNF monoclonal antibody or a soluble TNF receptor) or other biologic treatment for RA (such as anti-CD4 as abatacept, anti-CD20 as rituximab, anti-interleukin 6 as tocilizumab, or interleukin 1 receptor antagonist.

Part 2:

Subjects who were responders at the end of Part 1 were eligible for Part 2. Response in Part 1 was defined as a DAS28 ≤3.2 at the Week 39 visit and a DAS28 <2.6 at the Week 52 visit. Subjects were ineligible to participate in Part 2 of the study if they were non-responders at the end of Part 1.

Part 3:

Subjects who were responders at the end of Part 2 were eligible for Part 3. Response in Part 2 was defined as sustained remission (DAS28 <2.6) or low disease activity (2.6 ≤ DAS28 ≤ 3.2) at the Week 91 visit. Subjects were ineligible to participate in Part 3 of the study if they were non-responders at the end of Part 2.

Study Treatment:

Part 1: During the 52-week Part 1 portion of the study, ETN was administered as a once-weekly subcutaneous (SC) injection using the 50-mg prefilled syringe. During Part 1 of the study, open-label MTX capsules were administered orally once a week as a single oral dose or in divided doses on the same day, with optimal dosage between 10 mg and 20 mg once weekly. The minimum dose to stay in the study was 10 mg per week. According to the

principal Investigator clinical evaluation, optimization of MTX dosage to 25 mg once weekly was allowed but remained optional. Over the first 8 weeks of the study, the dosage of MTX was to be escalated by 5 mg once weekly at Week 2, Week 4, and Week 8 from a starting dosage of 10 mg once weekly to the maximum tolerated dosage of up to 25 mg unless the subject had no painful or swollen joints. If the subject did not tolerate the next dose level because of an adverse event (AE), the dose could have been lowered once by 5 mg to the previous dose. At the Week 2 visit (after 2 weeks of therapy), if the subject had an inadequate response (defined as any painful or swollen joints) and if the dose was tolerated, the weekly MTX dosage was to be increased to 15 mg once weekly. At the Week 4 visit (after 4 weeks of therapy), if the subject had an inadequate response (defined as any painful or swollen joints) and if the dose was tolerated, the weekly MTX dosage was to be increased to 20 mg once weekly. At the Week 8 visit, if the subject still had an inadequate response, the weekly MTX dosage could have been increased to 25 mg once weekly at the discretion of the investigator. Subjects receiving 25 mg once weekly could have the weekly MTX dosage reduced to 20 mg once weekly at any time during Part 1 of the study if 25 mg was not tolerated.

Part 2: Subjects who met the criteria for a response in Part 1 were randomized in a 1:1:1 ratio to 1 of 3 possible treatment arms:

- E25 by SC injection + MTX orally, both once weekly
- PBO SC injection + MTX orally
- PBO SC injection + PBO orally

Subjects who were assigned to either the MTX or PBO arms underwent a 2-week period of double-blind tapering of the ETN dose. In the first week of Part 2 the dose was 25 mg once weekly (ie, decreased from the 50-mg dose once weekly in Part 1), and in the second week it was decreased from 25 mg once weekly to placebo.

Subjects who were assigned to the PBO arm also underwent a 2- to 4-week period of double-blind tapering of the MTX dose. The duration of the period of dose tapering depended on the particular subject's MTX dose. MTX dose tapering was begun after the first week of ETN dose tapering.

Subjects with DAS28 >3.2 at Visit 10 (Week 56) or Visit 11 (Week 64) received a boost of corticosteroids. If at the subsequent visit the DAS28 remained >3.2, the subject was defined as a Part 2 non-responder and was withdrawn from the study.

At Visit 13 (Week 91), subjects in all 3 arms were classified as either Part 2 responders or Part 2 non-responders. Responders were subjects in sustained remission (DAS28 <2.6) or with low disease activity (2.6 ≤ DAS28 ≤ 3.2) at Visit 13 (Week 91). Non-responders were withdrawn from the study.

Part 3: ETN and matching placebo injections were stopped at Week 91. For Part 2 responders, the double-blind MTX treatment and placebo to MTX were tapered by 5 mg

weekly similar to the taper for the Part 2 MTX placebo arm to 0 mg by Week 95. According to the subject's optimal MTX dosage during Part 1 and 2, from 10 mg to 25 mg, the tapering period could last from 2 weeks to a maximum of 4 weeks.

For a subject having a 25-mg maximum tolerated dose of MTX during Part 1 and 2, MTX was administered once weekly in a single oral dose as follows:

- Week 91: 25 mg once weekly (ETN only was discontinued; MTX dosage remained the same as in Part 2 for the first week).
- Week 92: 20 mg once weekly.
- Week 93: 15 mg once weekly.
- Week 94: 10 mg once weekly.
- From Week 95 onwards: 0 mg.

Efficacy Endpoints:

Part 1 and Part 3: Primary Endpoint: Not applicable (only applicable for Part 2)

Part 2: Primary Endpoint:

The primary endpoint for this study was the proportion of subjects with sustained remission, defined as a DAS28 <2.6 at the Week 76 and Week 91 visits of Part 2 and no corticosteroid boost between the Week 52 and Week 64 visits.

Part 1: Secondary endpoints:

- Over the last 3 months of Part 1, a composite measure of complete response was defined as:
  - DAS28 <2.6 at the Week 39 and Week 52 visits (blinded assessor).
  - No radiographic progression over 52 weeks defined as mean change from Baseline in modified total Sharp score (mTSS) ≤0.5 (blinded assessor).
  - Health Assessment Questionnaire (HAQ) score ≤0.5 at the Week 39 and Week 52 visits.
- Remission (DAS44 <1.6).
- Low disease activity (DAS44 ≤ 2.4).
- Change from baseline in DAS_{44}, modified total Sharp score (mTSS), physician and patient global assessments of disease activity and pain (VAS).

- Proportion of subjects achieving a Patient Acceptable Symptom State (PASS).
- Proportion of subjects achieving ACR 20, ACR 50, ACR 70, and ACR 90 at each visit.
- Change from baseline in WPAI: RA endpoints.

Part 2: Secondary Endpoints:

For the ETN/MTX Phase 1 responder subgroup at the end of phase 1, the ETN 25 mg plus MTX arm were compared to the other treatment arms on similar endpoints to those described for phase 1.

- Over the last 3 months of Part 2, a composite measure of complete response defined as follows:
    - DAS28 <2.6 at the Week 76 and 91 Week visits.
    - No radiographic progression over 91 weeks, defined as mean change in mTSS ≤0.5.
    - HAQ ≤0.5 at the Week 76 and Week 91 visits.
- Remission (DAS44 <1.6).
- Low disease activity (DAS44 ≤ 2.4).
- Change from baseline in DAS_{44}, modified total Sharp score (mTSS), physician and patient global assessments of disease activity and pain (VAS).
- Proportion of subjects achieving a Patient Acceptable Symptom State (PASS).
- Proportion of subjects achieving ACR 20, ACR 50, ACR 70, and ACR 90 at each visit.
- Change from baseline in WPAI: RA endpoints.

Safety Evaluations:

Safety was assessed by the reporting of physical examination findings, vital signs, hematology, blood chemistry profiles, lipid profiles, urinalysis, premature withdrawal, AEs, Investigator-identified infections, serious AEs (SAEs), and serious Investigator-identified infections in all subjects who received at least 1 dose of study drug.

Statistical Methods:

Sample Size

In Part 2 of this study, a sample size of 55 subjects per group was required to detect with 90% probability (ie, 90% power) a difference of 30% in the sustained remission rates using a chi-square test at the 2-sided 5% significance level (ie, a 75% rate in the E25 + MTX arm versus a 45% rate in the placebo arm). With an allocation rate of 1:1:1, 165 subjects were required to be randomized in Part 2. Assuming a 52-week Part 1 responder rate of 55%, 300 subjects needed to be enrolled in Part 1 of the study.

Analysis Population

Efficacy data were analyzed in the modified intent-to-treat population, which included all subjects who took at least 1 dose of open-label investigational product. All subjects who provided a baseline assessment and at least 1 on-study assessment for an efficacy endpoint were included in the analysis of that endpoint.

A modified intent-to-treat (mITT) population was defined for each treatment phase. The Part 3 mITT population included all subjects who had completed Part 2 and had at least 1 Part 3 DAS28 evaluation (after Week 91). Additional analyses were performed for the Part 2 mITT population included all Part 2 subjects who have taken at least 1 dose of double-blind test article and ha at least 1 post-randomization DAS28 evaluation.

A safety population was defined for each treatment phase. The Part 3 safety population included all subjects who had completed Part 2 and had entered the MTX or placebo tapering phase.

A per-protocol (PP) population was defined for Part 2: The Part 2 PP population included those members of the Part 2 mITT population who have no major protocol violations that could potentially altered the interpretation of the efficacy analysis.

Time Points Analyzed

Data from each fixed time point (eg, Week 2, Week 4, etc) were analyzed. In addition, data from each subject's final on-therapy visit were analyzed. The final on-therapy analyses included data from subjects who were discontinued from the study before Week 52, including subjects who were discontinued for non-response at Week 39 or for unsatisfactory response per Investigator judgment.

Response Rates

For post-baseline proportions, p-values were applied to test the null hypothesis that the proportion, generally a response, was zero. Some subjects met, at baseline, the criteria for achieving certain endpoints (eg, HAQ score ≤0.5, PASS, RA-WIS). These data were analyzed using McNemar's test for no change from baseline in the response rate.

Change From Baseline

Change from baseline was analyzed for continuous and ordinal endpoints using paired t-tests. Significance tests for the null hypothesis of no significant change from baseline used a 2-sided α=0.05.

Analysis of Efficacy Parameters:

Efficacy in this subject population was evaluated throughout the course of the study. It was recommended that each subject be evaluated by the same qualified personnel throughout the study. All change from baseline analyses were performed using the true study baseline value (from the Baseline visit) and the Part 2 baseline value, ie, the Week 52 value, and also for this report from Part 3 baseline (Week 91). Within-group comparisons were performed for repeated measures and analyses based on models. Between-group comparisons were also performed. Repeated measures models were used for the majority of efficacy and health outcomes analyses; the models assumed that missing observations were missing completely at random, and no imputation for missing data was applied. Note that both longitudinal categorical models and logistic regression have the limitation that if one of the treatment groups has 0% or 100% responders at any time point included in the model, no estimates for odds ratios or p-values are produced for that model. In these cases estimates and p-values were indicated as non-estimable (NE) in the tables. In addition, for binary variables, a supporting set of tables presenting pairwise Fisher's exact tests were produced, to allow evaluation of statistical significance where the model could not. The analysis of the last observation under treatment served as a sensitivity analysis. For selected endpoints, an additional sensitivity analyses was performed that treated all subjects who dropped out as non-responders for a final on-therapy analysis; this approach was referred to as non-response imputation (NRI). This methodology was only applied to binary endpoints. The NRI analysis was the primary analysis for the DAS28 sustained remission endpoint and the composite measure of complete response endpoint; NRI imputation was a sensitivity analysis for other DAS28- and DAS44-based response endpoints and the ACR response endpoints.

Safety Evaluation: Safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography:

Part 1:

Of the 306 subjects who were entered in the study, 222 (72.55%) completed Part 1 and 84 (27.45%) did not complete Part 1. Of the 222 subjects who completed Part 1, 194 (63.40%) were randomized and continued to Part 2, 24 (7.84%) were non-responders at Week 52 and were not randomized, and 4 (1.31%) requested to not continue to Part 2. A complete description of subject disposition and demographic characteristics is given in Table 2 and Table 3.

Table 2. Summary of Subject Participation Status at the end of Part 1

Conclusion Status Reason	ETN 50 mg/MTX (N=306) n (%)
Total	306 (100.00)
Completed Part 1	222 (72.55)
Randomized	194 (63.40)
Part 1 non-responder at Week 52	24 (7.84)
Subject request	4 (1.31)
Did not complete Part 1[a]	84 (27.45)
Adverse event	20 (6.54)
Failure to return/lost to follow-up	2 (0.65)
Part 1 non-responder at Week 39	30 (9.80)
Protocol violation	10 (3.27)
Sponsor's decision	2 (0.65)
Subject request	13 (4.25)
Unsatisfactory response-efficacy per Investigator judgment	7 (2.29)

Two subjects were counted incorrectly as 'Did not complete Part 1' for the reason 'Part 1 non-responder at Week 39.' They will be corrected in subsequent reports as 'Completed Part 1, Part 1 non-responder at Week 52.

ETN = etanercept; MTX = methotrexate; N = total number of subjects entered the study; n=number of subjects in each criteria.

a. Total discontinued is the sum of individual reasons, as they are mutually exclusive by subject.

Table 3. Summary of Demographic and Baseline Characteristics – Part 1

Characteristic	ETN 50 mg/MTX (N=306)
Age (years)	
n	306
Mean (SD)	49.94 (13.70)
Min, Max	19.00, 80.40
Median	49.80
Sex, n (%)	
Female	213 (69.61)
Male	93 (30.39)
Race, n (%)	
White	286 (93.46)
Black	3 (0.98)
Asian	8 (2.61)
Other	9 (2.94)
Height (cm)	
n	306
Mean (SD)	166.85 (8.77)
Min, Max	140.00, 199.00
Median	166.00
Weight (kg)	
n	306
Mean (SD)	73.96 (15.78)
Min, Max	44.00, 130.00
Median	72.25
BMI, male (kg/m^2)	
n	93
Mean (SD)	27.41 (4.19)
Min, Max	17.75, 45.52
Median	27.28
BMI, female (kg/m^2)	
n	213
Mean (SD)	26.09 (5.16)
Min, Max	16.30, 41.34
Median	25.00
Duration of disease (months)	
n	306
Mean (SD)	6.53 (2.94)
Min, Max	0.43, 19.75
Median	6.34
Prior corticosteroids, n (%)	
Yes	123 (40.20)
No	183 (59.80)
Prior DMARDs, n (%)	
Yes	39 (12.75)
No	267 (87.25)
Prior NSAID, n (%)	
Yes	190 (62.09)
No	116 (37.91)
Prior MTX, n (%)	
No	306 (100.0)
Tobacco use, n (%)	
Yes	75 (24.51)
No	163 (53.27)

Table 3. Summary of Demographic and Baseline Characteristics – Part 1

Characteristic	ETN 50 mg/MTX (N=306)
Has stopped	68 (22.22)
Alcohol use, n (%)	
Yes	135 (44.12)
No	165 (53.92)
Has stopped	6 (1.96)

BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug; ETN = etanercept; Max = maximum; Min = minimum; MTX = methotrexate; N = total number of subjects entered the study; n = number of subjects in specific criteria; NSAID = non-steroidal anti-inflammatory drug; SD = standard deviation.

Part 2:

A total of 193 subjects were randomized in Part 2 of the study and 144 (74.6%) of these subjects completed Part 2. Subject disposition and demographic characteristics for Part 2 are presented in Table 4 and Table 5 respectively.

Table 4. Summary of Subject Participation Status at the End of Part 2

Conclusion Status Reason	Overall p-Value	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	PBO (N=65) n (%)	Total (N=193) n (%)
Total		63 (100.0)	65 (100.0)	65 (100.0)	193 (100.0)
Completed Part 2= Yes	0.0004	56 (88.89)	50 (76.92)	38 (58.46)	144 (74.61)
Continued to Part 3	0.0001	53 (84.13)	46 (70.77)	32 (49.23)	131 (67.88)
Part 2 non-responder	0.7898	3 (4.76)	4 (6.15)	5 (7.69)	12 (6.22)
Subject request	0.3717	0 (0.00)	0 (0.00)	1 (1.54)	1 (0.52)
Completed Part 2= No[a]	0.0004	7 (11.11)	15 (23.08)	27 (41.54)	49 (25.39)
Adverse event	0.1563	3 (4.76)	0 (0.00)	1 (1.54)	4 (2.07)
Failure to return/lost to follow-up	0.3717	0 (0.00)	0 (0.00)	1 (1.54)	1 (0.52)
Part 2 non-responder	0.1656	2 (3.17)	3 (4.62)	7 (10.77)	12 (6.22)
Protocol violation	0.1243	2 (3.17)	0 (0.00)	0 (0.00)	2 (1.04)
Subject request	0.6128	0 (0.00)	1 (1.54)	1 (1.54)	2 (1.04)
Unsatisfactory response-efficacy per Investigator judgement	0.0001	0 (0.00)	11 (16.92)	17 (26.15)	28 (14.51)

E25+MTX = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); N = total number of subjects entered the study; n = number of subjects in specific criteria; PBO = placebo etanercept + placebo methotrexate (group).

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject

Table 5. Summary of Demographic and Other Baseline Characteristics – Part 2

Characteristic Statistic	Overall p-Value	E25+MTX (N=63)	MTX (N=65)	PBO (N=65)	Total (N=193)
Age (years)					
n		63	65	65	193
Mean (SD)	0.6388	49.59 (14.96)	47.66 (14.13)	50.94 (14.24)	49.39 (14.43)
Min, max		(20.50, 78.60)	(19.00, 78.30)	(21.20, 80.40)	(19.00, 80.40)
Median		48.10	45.80	52.10	48.10
Sex, n (%)	0.0750				
Female		47 (74.60)	36 (55.38)	42 (64.62)	125 (64.77)
Male		16 (25.40)	29 (44.62)	23 (35.38)	68 (35.23)
Race, n (%)	0.8125				
White		60 (95.24)	62 (95.38)	61 (93.85)	183 (94.82)
Black		0 (0.00)	1 (1.54)	0 (0.00)	1 (0.52)
Asian		1 (1.59)	1 (1.54)	1 (1.54)	3 (1.55)
Other		2 (3.17)	1 (1.54)	3 (4.62)	6 (3.11)
Baseline height (cm)					
n		63	65	65	193
Mean (SD)	0.6943	167.63 (8.62)	168.49 (10.25)	166.55 (8.57)	167.56 (9.17)
Min, max		(146, 199)	(140, 196)	(147, 183)	(140, 199)
Median		167	168	165	167
Baseline weight (kg)					
n		63	65	65	193
Mean (SD)	0.9937	72.75 (14.93)	73.14 (16.35)	72.34 (15.89)	72.74 (15.66)
Min, max		(50, 110)	(44.5, 110)	(44, 130)	(44, 130)
Median		70.0	73.0	70.4	71.7
Baseline BMI (kg/m^2) - Male					
n		16	29	23	68
Mean (SD)	0.9540	27.87 (4.31)	27.57 (3.06)	27.37 (5.98)	27.58 (4.46)
Min, max		(21.13, 36.00)	(22.70, 35.43)	(17.75, 45.52)	(17.75, 45.52)
Median		27.77	27.28	26.83	27.28
Baseline BMI (kg/m^2) - Female					
n		47	36	42	125
Mean (SD)	0.9540	25.13 (4.53)	23.92 (4.20)	25.26 (4.30)	24.83 (4.36)
Min, max		(19.33, 36.84)	(16.30, 33.66)	(17.85, 39.43)	(16.30, 39.43)
Median		23.80	23.63	24.82	24.22
Duration of disease symptoms (months)					
n		63	65	65	193
Mean (SD)	0.7855	6.54 (3.07)	6.85 (2.66)	7.06 (2.84)	6.82 (2.85)
Min, max		(1.15, 11.50)	(1.61, 11.33)	(0.43, 11.37)	(0.43, 11.50)
Median		6.51	6.51	7.36	6.57
Duration of primary diagnosis (months)					
n		63	65	65	193
Mean (SD)	0.5965	2.88 (2.24)	3.40 (2.85)	3.50 (3.03)	3.26 (2.73)
Min, max		(0.30, 9.43)	(0.33, 9.82)	(0.03, 11.37)	(0.03, 11.37)
Median		2.10	2.14	2.60	2.30
Prior corticosteroids, n (%)	0.0278				
Yes		26 (41.27)	19 (29.23)	34 (52.31)	79 (40.93)
No		37 (58.73)	46 (70.77)	31 (47.69)	114 (59.07)
Prior DMARDs, n (%)	0.0586				

Table 5. Summary of Demographic and Other Baseline Characteristics – Part 2

Characteristic Statistic	Overall p-Value	E25+MTX (N=63)	MTX (N=65)	PBO (N=65)	Total (N=193)
Yes		8 (12.70)	8 (12.31)	17 (26.15)	33 (17.10)
No		55 (87.30)	57 (87.69)	48 (73.85)	160 (82.90)
Prior NSAID, n (%)	0.0836				
Yes		42 (66.67)	49 (75.38)	37 (56.92)	128 (66.32)
No		21 (33.33)	16 (24.62)	28 (43.08)	65 (33.68)
Prior methotrexate, n (%)					
No		63 (100.0)	65 (100.0)	65 (100.0)	193 (100.0)
Tobacco use, n (%)	0.5168				
Yes		13 (20.63)	15 (23.08)	10 (15.38)	38 (19.69)
No		38 (60.32)	32 (49.23)	36 (55.38)	106 (54.92)
Has stopped		12 (19.05)	18 (27.69)	19 (29.23)	49 (25.39)
Alcohol use, n (%)	0.4081				
Yes		27 (42.86)	29 (44.62)	26 (40.00)	82 (42.49)
No		36 (57.14)	33 (50.77)	38 (58.46)	107 (55.44)
Has stopped		0 (0.00)	3 (4.62)	1 (1.54)	4 (2.07)

BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug;
E25+MTX = etanercept 25 mg + methotrexate (group); max = maximum; min = minimum; MTX = placebo etanercept + methotrexate (group); N = total number of subjects entered the study; n = number of subjects in specific criteria; NSAID = non-steroidal anti-inflammatory drug; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation.

Part 3: A total of 131 subjects were enrolled in Part 3 of the study; 83 (63.4%) of these subjects completed Part 3. Subject disposition and demographic characteristics for Part 2 are presented in Table 6 and Table 7, respectively.

Table 6. Summary of Subject Participation Status at the end of Part 3

Conclusion Status Reason	Overall p-Value	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)	Total (N=131)
Total		53 (100.0)	46 (100.0)	32 (100.0)	131 (100.0)
Complete Part 3=Yes	0.2820	31 (58.49)	28 (60.87)	24 (75.00)	83 (63.36)
Complete Part 3=No[a]	0.2820	22 (41.51)	18 (39.13)	8 (25.00)	48 (36.64)
Adverse event	0.5380	5 (9.43)	4 (8.70)	1 (3.13)	10 (7.63)
Failure to return/lost to follow-up	0.2244	2 (3.77)	0 (0.00)	0 (0.00)	2 (1.53)
Part 2 non responder	0.0471	0 (0.00)	1 (2.17)	3 (9.38)	4 (3.05)
Subject request	0.4363	1 (1.89)	2 (4.35)	0 (0.00)	3 (2.29)
Unsatisfactory response-efficacy per Investigator judgement	0.3056	14 (26.42)	11 (23.91)	4 (12.50)	29 (22.14)

Part 2 non-responder is defined as a subject who had a DAS28 score of >3.2 at visit 13. Four subjects met this criterion in Part 2 and did not follow the protocol by continuing into Part 3. These subjects were later discontinued during Part 3 for this reason.
E25+MTX = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); N = total number of subjects entered the study; PBO = placebo etanercept + placebo methotrexate (group).
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 7. Summary of Demographic and Other Baseline Characteristics – Part 3

Characteristic Statistic	Overall p-Value	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)	Total (N=131)
Age (years)					
n		53	46	32	131
Mean (SD)	0.6680	48.88 (15.30)	46.83 (15.34)	51.35 (17.00)	48.76 (15.72)
Min, max		(20.50, 75.30)	(19.00, 78.30)	(21.20, 80.40)	(19.00, 80.40)
Median		48.10	44.75	54.40	48.00
Sex, n (%)	0.2024				
Female		40 (75.47)	27 (58.70)	22 (68.75)	89 (67.94)
Male		13 (24.53)	19 (41.30)	10 (31.25)	42 (32.06)
Race, n (%)	0.1889				
White		52 (98.11)	44 (95.65)	30 (93.75)	126 (96.18)
Black		0 (0.00)	1 (2.17)	0 (0.00)	1 (0.76)
Asian		1 (1.89)	1 (2.17)	0 (0.00)	2 (1.53)
Other		0 (0.00)	0 (0.00)	2 (6.25)	2 (1.53)
Baseline height (cm)					
n		53	46	32	131
Mean (SD)	0.9111	167.71 (8.69)	167.65 (10.35)	166.31 (8.45)	167.35 (9.20)
Min, max		(146.00, 199.00)	(140.00, 196.00)	(147.00, 183.00)	(140.00, 199.00)
Median		167.00	167.15	164.50	167.00
Baseline weight (kg)					
n		53	46	32	131
Mean (SD)	0.9825	72.80 (15.16)	72.22 (16.32)	71.41 (13.57)	72.26 (15.11)
Min, max		(52.00, 110.00)	(44.50, 110.00)	(49.00, 109.00)	(44.50, 110.00)
Median		70.00	71.00	71.90	71.70
Baseline BMI (kg/m^2) - Male					
n		13	19	10	42
Mean (SD)	0.9828	28.38 (4.33)	27.22 (2.94)	26.93 (3.42)	27.51 (3.49)
Min, max		(21.13, 36.00)	(22.70, 32.74)	(20.59, 32.55)	(20.59, 36.00)
Median		27.78	27.03	26.62	27.28
Baseline BMI (kg/m^2) - Female					
n		40	27	22	89
Mean (SD)	0.9828	24.99 (4.47)	24.25 (4.42)	25.17 (3.98)	24.81 (4.31)
Min, max		(19.33, 36.84)	(16.30, 33.66)	(18.00, 33.37)	(16.30, 36.84)
Median		23.61	24.18	24.82	24.18
Duration of disease symptoms (months)					
n		53	46	32	131
Mean (SD)	0.9695	6.61 (3.01)	6.88 (2.77)	6.67 (2.54)	6.72 (2.80)
Min, max		(1.15, 11.50)	(1.61, 11.27)	(1.48, 10.71)	(1.15, 11.50)
Median		6.51	7.41	7.28	6.57
Duration of primary diagnosis (months)					
n		53	46	32	131
Mean (SD)	0.5446	2.96 (2.26)	3.60 (2.92)	2.83 (2.54)	3.15 (2.58)
Min, max		(0.30, 9.43)	(0.33, 9.76)	(0.26, 10.15)	(0.26, 10.15)
Median		2.10	2.25	1.99	2.10
Prior corticosteroids, n (%)	0.2254				
Yes		21 (39.62)	13 (28.26)	15 (46.88)	49 (37.40)
No		32 (60.38)	33 (71.74)	17 (53.13)	82 (62.60)

Table 7. Summary of Demographic and Other Baseline Characteristics – Part 3

Characteristic Statistic	Overall p-Value	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)	Total (N=131)
Prior DMARDs, n (%)	0.2566				
Yes		8 (15.09)	7 (15.22)	9 (28.13)	24 (18.32)
No		45 (84.91)	39 (84.78)	23 (71.88)	107 (81.68)
Prior NSAID, n (%)	0.1818				
Yes		36 (67.92)	35 (76.09)	18 (56.25)	89 (67.94)
No		17 (32.08)	11 (23.91)	14 (43.75)	42 (32.06)
Prior methotrexate, n (%)	N/A				
No		53 (100.0)	46 (100.0)	32 (100.0)	131 (100.0)
Tobacco use, n (%)	0.8314				
Yes		11 (20.75)	11 (23.91)	5 (15.63)	27 (20.61)
No		31 (58.49)	24 (52.17)	21 (65.63)	76 (58.02)
Has stopped		11 (20.75)	11 (23.91)	6 (18.75)	28 (21.37)
Alcohol use, n (%)	0.2079				
Yes		24 (45.28)	21 (45.65)	14 (43.75)	59 (45.04)
No		29 (54.72)	22 (47.83)	18 (56.25)	69 (52.67)
Has stopped		0 (0.00)	3 (6.52)	0 (0.00)	3 (2.29)

BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug;
E25+MTX = etanercept 25 mg+methotrexate (group); max = maximum; min = minimum; MTX = placebo etanercept + methotrexate (group); N = total number of subjects entered the study; n = number of subjects in specific criteria; N/A = not applicable; NSAID = non-steroidal anti-inflammatory drug; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation.

Efficacy Results:

Part 1 and Part 3: Primary Efficacy Results

The primary endpoint for this study was not analyzed as the variables for this analysis occur in Part 2 of the study.

Part 2: Primary Efficacy Results:

The primary endpoint for this study was the proportion of subjects with sustained remission, defined as a DAS28 <2.6 at the Week 76 and Week 91 visits of Part 2 without requiring a corticosteroid boost between the Week 52 and Week 64 visits, where the requirement for a corticosteroid boost was defined as a value of DAS28 >3.2 at either the Week 56 or Week 64 visit. Table 8 and Table 9 present the results for both mITT population and PP population, respectively.

The hypothesis of primary interest was the superiority of E25+MTX compared with PBO. A statistically significantly greater proportion of subjects in the E25+MTX treatment group had sustained remission at Week 76 and Week 91 compared with the PBO group (63.5% vs 23.1%, p<0.0001; OR [95% confidence interval {CI}]: 5.80 [2.7, 12.5]; Table 8).

A statistically significantly greater proportion of subjects in the E25+MTX treatment group had sustained remission at Week 76 and Week 91 compared with the MTX group (63.5% vs 40.0%, p=0.0085; OR [95% CI]: 2.61 [1.3, 5.3]).

A statistically significantly greater proportion of subjects in the MTX treatment group had sustained remission at Week 76 and Week 91 compared with the PBO group (40.0% vs 23.1%, p=0.0397; OR [95% CI]: 2.22 [1.0, 4.8]).

Table 8. Number (%) of Subjects With Sustained Remission at Week 76 and Week 91 Who Did Not Require a Corticosteroid Boost From Week 52 to Week 64, mITT Population – Part 2

Treatment Group			Pairwise Comparisons[a]		
E25+MTX n/N (%) 95% CI[b]	MTX n/N (%) 95% CI[b]	PBO n/N (%) 95% CI[b]	E25 vs MTX P-Value OR (95% CI)	E25 vs PBO P-Value OR (95% CI)	MTX vs PBO p-Value OR (95% CI)
40/63 (63.5) 50.4, 75.3	26/65 (40.0) 28.0, 52.9	15/65 (23.1) 13.5, 35.2	0.0085 2.61 (1.3, 5.3)	<0.0001 5.80 (2.7, 12.5)	0.0397 2.22 (1.0, 4.8)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg+methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N = total number of subjects entered the study; n = number of subjects in specific criteria; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group).

a. Odds ratios, p-values, and 95% CIs are based on a logistic regression model with treatment as the only factor.
b. 95% CIs on proportions are based on the binomial exact procedure.

The results of an analysis using the PP population support the primary efficacy analysis (Table 9). In this analysis, the proportions of subjects in the MTX and PBO treatment groups with sustained remission at Week 76 and Week 91 were significantly different in favor of the MTX group (41.7% vs 24.1%, p=0.0450).

Table 9. Number (%) of Subjects With Sustained Remission at Week 76 and Week 91 Who Did Not Require a Corticosteroid Boost From Week 52 to Week 64, Per Protocol Population – Part 2

Treatment Group			Pairwise Comparisons[a]		
E25+MTX n/N (%) 95% CI[b]	MTX n/N (%) 95% CI[b]	PBO n/N (%) 95% CI[b]	E25 vs MTX P-Value OR (95% CI)	E25 vs PBO P-Value OR (95% CI)	MTX vs PBO P-Value OR (95% CI)
38/55 (69.1) 55.2, 80.9	25/60 (41.7) 29.1, 55.1	14/58 (24.1) 13.9, 37.2	0.0036 3.13 (1.5, 6.7)	<0.0001 7.03 (3.1, 16.1)	0.0450 2.24 (1.0, 4.9)

CI=confidence interval; E25+MTX or E25=etanercept 25 mg+methotrexate (group); mITT=modified intent-to-treat; MTX=placebo etanercept + methotrexate (group); N=total number of subjects entered the study; n=number of subjects in specific criteria; OR=odds ratio; PBO=placebo etanercept + placebo methotrexate (group).

a. Odds ratios, p-values, and 95% CIs are based on a logistic regression model with treatment as the only factor.
b. 95% CIs on proportions are based on the binomial exact procedure

Secondary Efficacy Results:

Complete Response: Part 1:

Table 10 presents the proportion of subjects who achieved a complete response at the end of Part 1 which was 29.1% (95% [CI]: 24.1, 34.5; p<0.0001). In this analysis, subjects who discontinued from the study prior to Week 52 were considered non-responders at Week 52.

Table 10. Proportion of Subjects Achieving a Complete Response – Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-value[a]
End of Part 1	89/306	29.1% (24.1, 34.5)	<0.0001

CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion is significantly different from 0.

Table 11 presents number (%) of subjects with a complete response, in mITT Population in Part 2. Results in the PP population were similar.

Table 11. Number (%) of Subjects With a Complete Response, mITT Population - Part 2

Treatment Group			Pairwise Comparisons[a]		
E25+MTX n/N (%) 95% CI[b]	MTX n/N (%) 95% CI[b]	PBO n/N (%) 95% CI[b]	E25 vs MTX p-Value OR (95% CI)	E25 vs PBO p-Value OR (95% CI)	MTX vs PBO p-Value OR (95% CI)
36/63 (57.1) 30.5, 56.0	19/65 (29.2) 58.2, 81.4	7/65 (10.8) 79.1, 95.6	0.0017 3.23 (1.6, 6.7)	<0.0001 11.05 (4.4, 28.0)	0.0111 3.42 (1.3, 8.8)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group).
a. Odds ratios, p-values, and 95% CIs were based on a logistic regression model with treatment as the only factor.
b. 95% CIs on proportions were based on the binomial exact procedure.

Remission (DAS44 <1.6):

Part 1:

The proportion of subjects who achieved DAS44 remission (ie, DAS44 <1.6) was statistically significantly different from 0 at all time points (Table 12). At Week 52, the proportion of subjects with DAS44 remission was 87.3% (95% CI: 82.2, 91.4). The proportion of subjects with DAS44 remission at their final on-therapy visit was 69.2% (95% CI: 63.7, 74.3).

Table 12. Proportion of Subjects Achieving DAS44 Remission – Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-value[a]
Baseline	1/306	0.3% (0.0, 1.8)	<0.0001
Week 2	13/297	4.4% (2.4, 7.4)	<0.0001
Week 4	48/293	16.4% (12.3, 21.1)	<0.0001
Week 8	81/293	27.6% (22.6, 33.1)	<0.0001
Week 13	95/282	33.7% (28.2, 39.5)	<0.0001
Week 26	142/276	51.4% (45.4, 57.5)	<0.0001
Week 39	174/259	67.2% (61.1, 72.9)	<0.0001
Week 52	193/221	87.3% (82.2, 91.4)	<0.0001
Final on therapy visit	211/305	69.2% (63.7, 74.3)	<0.0001

CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion is significantly different from 0.

Part 2:

Table 13 and Table 14 present results for DAS44 remission and DAS44 remission (NRI) respectively in mITT population for Part 2.

Table 13. Number (%) of Subjects With DAS44 Remission, mITT Population - Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX n/N (%) 95% CI	MTX n/N (%) 95% CI	PBO n/N (%) 95% CI	E25 vs MTX p-Value OR (95% CI)	E25 vs PBO p-Value OR (95% CI)	MTX vs PBO p-Value OR (95% CI)
Week 52[b]	60/63 (95.2) 86.7, 99.0	62/65 (95.4) 87.1, 99.0	60/65 (92.3) 83.0, 97.5	0.9687 NE	0.4974 NE	0.4700 NE
Week 56	52/63 (82.5) 70.9, 90.9	52/65 (80.0) 68.2, 88.9	47/63 (74.6) 62.1, 84.7	0.7130 1.18 (0.5, 2.9)	0.2306 1.68 (0.7, 3.9)	0.3972 1.43 (0.6, 3.2)
Week 64	54/62 (87.1) 76.1, 94.3	44/63 (69.8) 57.0, 80.8	25/60 (41.7) 29.1, 55.1	0.0155 3.10 (1.2, 7.7)	<0.0001 10.08 (4.1, 25.0)	0.0017 3.25 (1.6, 6.8)
Week 76	51/60 (85.0) 73.4, 92.9	42/57 (73.7) 60.3, 84.5	24/46 (52.2) 36.9, 67.1	0.0643 2.36 (1.0, 5.8)	<0.0001 6.74 (2.7, 16.8)	0.0091 2.86 (1.3, 6.3)
Week 91	48/57 (84.2) 72.1, 92.5	39/52 (75.0) 61.1, 86.0	23/38 (60.5) 43.4, 76.0	0.0788 2.17 (0.9, 5.2)	0.0007 4.57 (1.9, 11.0)	0.0676 2.10 (0.9, 4.7)
Final on therapy[b]	51/63 (81.0) 69.1, 89.8	40/65 (61.5) 48.6, 73.3	24/65 (36.9) 25.3, 49.8	0.0171 2.66 (1.2, 5.9)	<0.0001 7.26 (3.2, 16.3)	0.0055 2.73 (1.3, 5.6)

CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; E25+MTX or E25 = etanercept 25 mg+methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept+methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; NE = not estimable; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group), vs = versus.
a. Odds ratios and p-values for pairwise treatment comparisons at Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for treatment, visit, and interaction of treatment and visit.
b. Baseline and final on-therapy comparisons were based on a model with treatment only.

Table 14. Number (%) of Subjects With DAS44 Remission (NRI), mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX n/N (%) 95% CI	MTX n/N (%) 95% CI	PBO n/N (%) 95% CI	E25 vs MTX p-Value	E25 vs PBO p-Value	MTX vs PBO p-Value
Week 52	60/63 (95.2) 86.7, 99.0	62/65 (95.4) 87.1, 99.0	60/65 (92.3) 83.0, 97.5	1.0000	0.7179	0.7178
Week 56	52/63 (82.5) 70.9, 90.9	52/65 (80.0) 68.2, 88.9	47/65 (72.3) 59.8, 82.7	0.8219	0.2068	0.4107
Week 64	54/63 (85.7) 74.6, 93.3	44/65 (67.7) 54.9, 78.8	25/65 (38.5) 26.7, 51.4	0.0214	<0.0001	0.0015
Week 76	51/63 (81.0) 69.1, 89.8	42/65 (64.6) 51.8, 76.1	24/65 (36.9) 25.3, 49.8	0.0478	<0.0001	0.0027
Week 91	48/63 (76.2) 63.8, 86.0	39/65 (60.0) 47.1, 72.0	23/65 (35.4) 23.9, 48.2	0.0593	<0.0001	0.0082

CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept+methotrexate (group); NRI=non-response imputation; PBO=placebo etanercept + placebo methotrexate (group), vs =versus.

a. P-values for pairwise treatment comparisons at Week 52 to Week 91 visits are based on a 2-sided pairwise Fisher's exact test.

Low Disease Activity (DAS44 ≤2.4):

Part 1:

Table 15 presents the proportion of subjects who achieved DAS44 low disease activity (ie, DAS44 ≤2.4) which was statistically significantly different from 0 at all time points. At Week 52, the proportion of subjects with DAS44 low disease activity was 96.8% (95% CI: 93.6, 98.7). The proportion of subjects with DAS44 low disease activity at their final on-therapy visit was 81.6% (95% CI: 76.8, 85.8).

Table 15. Proportion of Subjects Achieving DAS44 Low Disease Activity – Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-value[a]
Baseline	6/306	2.0% (0.7, 4.2)	<0.0001
Week 2	67/297	22.6% (17.9, 27.7)	<0.0001
Week 4	122/293	41.6% (35.9, 47.5)	<0.0001
Week 8	157/293	53.6% (47.7, 59.4)	<0.0001
Week 13	194/282	68.8% (63.0, 74.2)	<0.0001
Week 26	210/276	76.1% (70.6, 81.0)	<0.0001
Week 39	236/259	91.1% (87.0, 94.3)	<0.0001
Week 52	214/221	96.8% (93.6, 98.7)	<0.0001
Final on therapy visit	249/305	81.6% (76.8, 85.8)	<0.0001

CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion was significantly different from 0.

Part 2:

Table 16 and Table 17 present results for DAS44 low disease activity and DAS44 low disease activity (NRI) respectively in mITT population for Part 2.

Table 16. Number (%) of Subjects With DAS44 Low Disease Activity, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX n/N (%) 95% CI	MTX n/N (%) 95% CI	PBO n/N (%) 95% CI	E25 vs MTX p-Value OR (95% CI)	E25 vs PBO p-Value OR (95% CI)	MTX vs PBO p-Value OR (95% CI)
Week 52[b]	63/63 (100) 94.3, 100	65/65 (100) 94.5, 100	65/65 (100) 94.5, 100	NE	NE	NE
Week 56	62/63 (98.4) 91.5, 100	60/65 (92.3) 83.0, 97.5	54/63 (85.7) 74.6, 93.3	0.1391 5.17 (0.6, 45.5)	0.0260 10.75 (1.3, 86.9)	0.2078 2.08 (0.7, 6.5)
Week 64	61/62 (98.4) 91.3, 100	52/63 (82.5) 70.9, 90.9	38/60 (63.3) 49.9, 75.4	0.0133 13.86 (1.7, 111.0)	0.0005 37.59 (4.8, 291.7)	0.0160 2.71 (1.2, 6.1)
Week 76	57/60 (95.0) 86.1, 99.0	54/57 (94.7) 85.4, 98.9	37/46 (80.4) 66.1, 90.6	0.9175 1.09 (0.2, 5.5)	0.0222 4.87 (1.3, 18.9)	0.0274 4.47 (1.2, 16.9)
Week 91	56/57 (98.2) 90.6, 100	47/52 (90.4) 79.0, 96.8	33/38 (86.8) 71.9, 95.6	0.0548 7.56 (1.0, 59.5)	0.0166 12.18 (1.6, 94.2)	0.3619 1.61 (0.6, 4.5)
Final on therapy[b]	60/63 (95.2) 86.7, 99.0	50/65 (76.9) 64.8, 86.5	35/65 (53.8) 41.0, 66.3	0.0067 6.00 (1.6, 21.9)	<0.0001 17.14 (4.9, 60.3)	0.0065 2.86 (1.3, 6.1)

CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; NE = not estimable; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group).
a. Odds ratios and p-values for pairwise treatment comparisons at Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for treatment, visit, and interaction of treatment and visit.
b. Baseline and final on-therapy comparisons were based on a model with treatment only.

Table 17. Number (%) of Subjects With DAS44 Low Disease Activity (NRI), mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX n/N (%) 95% CI	MTX n/N (%) 95% CI	PBO n/N (%) 95% CI	E25 vs MTX p-Value	E25 vs PBO Pp-Value	MTX vs PBO p-Value
Week 52	63/63 (100) 94.3, 100	65/65 (100) 94.5, 100	65/65 (100) 94.5, 100			
Week 56	62/63 (98.4) 91.5, 100	60/65 (92.3) 83.0, 97.5	54/65 (83.1) 71.7, 91.2	0.2079	0.0043	0.1807
Week 64	61/63 (96.8) 89.0, 99.6	52/65 (80.0) 68.2, 88.9	38/65 (58.5) 45.6, 70.6	0.0046	<0.0001	0.0130
Week 76	57/63 (90.5) 80.4, 96.4	54/65 (83.1) 71.7, 91.2	37/65 (56.9) 44.0, 69.2	0.2987	<0.0001	0.0020
Week 91	56/63 (88.9) 78.4, 95.4	47/65 (72.3) 59.8, 82.7	33/65 (50.8) 38.1, 63.4	0.0250	<0.0001	0.0187

CI = confidence interval; DAS44=Disease Activity Score based on a 44-joint count; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; NRI = non-response imputation; PBO = placebo etanercept + placebo methotrexate (group).

a. P-values for pairwise treatment comparisons at Week 52 to Week 91 visits were based on a 2-sided pairwise Fisher's exact test.

Change From Baseline at Each Visit in DAS44:

Part 1:

The mean change from baseline in DAS44 was statistically significant at all time points (Table 18). At Week 52, the mean (standard deviation [SD]) change from baseline in DAS44 was -3.4 (1.2). The mean (SD) change from baseline in DAS44 at the final on-therapy visit was -3.0 (1.3).

Table 18. Change From Baseline in DAS44 – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	306	-	-
	Mean	4.7	-	-
	SD	1.2	-	-
	Minimum	1.4	-	-
	Maximum	9.3	-	-
	Median	4.6	-	-
Week 2	N	297	297	-
	Mean	3.4	-1.3	<0.0001
	SD	1.3	0.9	-
	Minimum	0.5	-4.1	-
	Maximum	8.6	1.2	-
	Median	3.2	-1.3	-
Week 4	N	293	293	-
	Mean	2.8	-1.9	<0.0001
	SD	1.3	1.1	-
	Minimum	0.4	-5.9	-
	Maximum	8.6	1.6	-
	Median	2.7	-1.8	-
Week 8	N	293	293	-
	Mean	2.4	-2.3	<0.0001
	SD	1.2	1.1	-
	Minimum	0.2	-6.1	-
	Maximum	7.8	0.7	-
	Median	2.3	-2.2	-
Week 13	N	282	282	-
	Mean	2.1	-2.5	<0.0001
	SD	1.2	1.2	-
	Minimum	0.0	-6.2	-
	Maximum	7.7	0.7	-
	Median	2.0	-2.5	-
Week 26	N	276	276	-
	Mean	1.8	-2.9	<0.0001
	SD	1.1	1.2	-
	Minimum	0.0	-6.9	-
	Maximum	7.4	0.4	-
	Median	1.6	-2.8	-
Week 39	N	259	259	-
	Mean	1.4	-3.2	<0.0001
	SD	0.9	1.2	-
	Minimum	0.1	-5.9	-
	Maximum	5.9	-0.1	-
	Median	1.2	-3.1	-
Week 52	N	221	221	-
	Mean	1.1	-3.4	<0.0001
	SD	0.5	1.2	-
	Minimum	0.0	-6.5	-
	Maximum	3.5	0.3	-
	Median	1.0	-3.4	-
Final on therapy visit	N	305	305	-
	Mean	1.6	-3.0	<0.0001

Table 18. Change From Baseline in DAS44 – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
	SD	1.3	1.3	-
	Minimum	0.0	-6.9	-
	Maximum	7.4	0.4	-
	Median	1.2	-3.1	-

DAS44 = Disease Activity Score based on a 44-joint count; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation.
a. Paired t-test.

Part 2:

The mean increase in DAS44 from the Part 2 baseline (ie, Week 52) was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at all post-Week 52 time points, and compared with the MTX group at Week 64, Week 91, and at the final on-therapy visit (Table 19).

Table 19. DAS44: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX, n Raw Mean (SD) Adj Change (SE)	MTX, n Raw Mean (SD) Adj Change (SE)	PBO, n Raw Mean (SD) Adj Change (SE)	E25 vs MTX p-Value Diff (95% CI)	E25 vs PBO p-Value Diff (95% CI)	MTX vs PBO p-Value Diff (95% CI)
Week 52[a]	63 1.0 (0.4)	65 1.0 (0.4)	65 1.1 (0.4)	0.5345	0.3738	0.1287
Week 56	63 1.1 (0.5) 0.1 (0.09)	65 1.2 (0.8) 0.2 (0.09)	63 1.4 (0.9) 0.4 (0.09)	0.3750 -0.11 (-0.3, 0.1)	0.0178 -0.29 (-0.5, -0.1)	0.1314 -0.18 (-0.4, 0.1)
Week 64	62 1.1 (0.5) 0.0 (0.13)	63 1.5 (1.0) 0.6 (0.12)	60 2.2 (1.3) 1.2 (0.13)	0.0037 -0.52 (-0.9, -0.2)	<0.0001 -1.15 (-1.5, -0.8)	0.0006 -0.63 (-1.0, -0.3)
Week 76	60 1.1 (0.6) 0.1 (0.10)	57 1.3 (0.7) 0.4 (0.11)	46 1.8 (1.0) 1.0 (0.12)	0.0595 -0.28 (-0.6, 0.0)	<0.0001 -0.89 (-1.2, -0.6)	0.0002 -0.60 (-0.9, -0.3)
Week 91	57 1.1 (0.6) 0.2 (0.13)	52 1.4 (0.8) 0.6 (0.14)	38 1.7 (1.2) 1.2 (0.15)	0.0183 -0.46 (-0.8, -0.1)	<0.0001 -1.07 (-1.5, -0.7)	0.0034 -0.62 (-1.0, -0.2)
Final on therapy[b]	63 1.2 (0.7) 0.2 (0.14)	65 1.7 (1.1) 0.7 (0.14)	65 2.5 (1.5) 1.5 (0.14)	0.0111 -0.52 (-0.9, -0.1)	<0.0001 -1.27 (-1.7, -0.9)	0.0002 -0.75 (-1.2, -0.4)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; DAS44 = Disease Activity Score based on a 44-joint count; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE=standard error.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Change From Baseline in Physician Global Assessment of Disease Activity:

Part 1:

The mean change from baseline in the Physician's Global Assessment of Disease Activity score was statistically significant at all time points (Table 20). At Week 52, the mean (SD) change from baseline in the physician global assessment of disease activity score was -49.2 (17.2). The mean (SD) change from baseline in the physician global assessment of disease activity score at the final on-therapy visit was -45.0 (19.8).

Part 2:

The mean increase in the Physician's Global Assessment of Disease Activity score from the Part 2 baseline (ie, Week 52) was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at all post-Week 52 time points, and compared with the MTX group at Week 64, Week 76, Week 91, and at the final on-therapy visit (Table 21).

Table 20. Change From Baseline in Physician Global Assessment of Disease Activity Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	306	-	-
	Mean	57.5	-	-
	SD	16.2	-	-
	Minimum	8.0	-	-
	Maximum	99.0	-	-
	Median	57.5	-	-
Week 2	N	300	300	-
	Mean	36.4	-21.0	<0.0001
	SD	18.6	18.2	-
	Minimum	1.0	-71.0	-
	Maximum	98.0	47.0	-
	Median	35.0	-21.0	-
Week 4	N	299	299	-
	Mean	28.3	-29.0	<0.0001
	SD	19.0	19.7	-
	Minimum	0.0	-86.0	-
	Maximum	96.0	37.0	-
	Median	26.0	-29.0	-
Week 8	N	294	294	-
	Mean	22.4	-34.8	<0.0001
	SD	17.3	19.9	-
	Minimum	0.0	-95.0	-
	Maximum	75.0	24.0	-
	Median	18.0	-36.0	-
Week 13	N	284	284	-
	Mean	18.4	-38.7	<0.0001
	SD	16.5	20.0	-
	Minimum	0.0	-95.0	-
	Maximum	86.0	20.0	-
	Median	13.0	-39.0	-
Week 26	N	277	277	-
	Mean	14.5	-42.4	<0.0001
	SD	15.4	18.9	-
	Minimum	0.0	-91.0	-
	Maximum	70.0	9.0	-
	Median	8.0	-43.0	-
Week 39	N	260	260	-
	Mean	9.9	-46.5	<0.0001
	SD	12.2	18.5	-
	Minimum	0.0	-96.0	-
	Maximum	68.0	51.0	-
	Median	5.0	-47.0	-
Week 52	N	223	223	-
	Mean	6.0	-49.2	<0.0001
	SD	7.9	17.2	-
	Minimum	0.0	-95.0	-
	Maximum	54.0	8.0	-
	Median	3.0	-49.0	-
Final on therapy visit	N	305	305	-

Table 20. Change From Baseline in Physician Global Assessment of Disease Activity Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
	Mean	12.5	-45.0	<0.0001
	SD	16.6	19.8	-
	Minimum	0.0	-95.0	-
	Maximum	80.0	10.0	-
	Median	5.0	-47.0	-

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation.
a. Paired t-test.

Table 21. Physician's Global Assessment of Disease Activity: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

Time Point	Treatment Group			Pairwise Comparisons[a]		
	E25+MTX, n Raw Mean (SD) Adj Change (SE)	MTX, n Raw Mean (SD) Adj Change (SE)	PBO, n Raw Mean (SD) Adj Change (SE)	E25 vs MTX p-Value Diff (95% CI)	E25 vs PBO p-Value Diff (95% CI)	MTX vs PBO p-Value Diff (95% CI)
Week 52[a]	63 5.0 (5.3) -	65 4.2 (4.9) -	65 6.3 (8.0) -	0.4951 -	0.2146 -	0.0534 -
Week 56	63 5.5 (6.2) 0.4 (1.44)	65 7.7 (12.6) 2.9 (1.43)	65 12.2 (15.1) 6.5 (1.43)	0.2052 -2.58 (-6.6, 1.4)	0.0028 -6.15 (-10.2, -2.1)	0.0792 -3.58 (-7.6, 0.4)
Week 64	62 6.0 (7.4) 0.9 (2.37)	63 11.6 (16.7) 8.1 (2.35)	62 23.6 (26.0) 18.5 (2.36)	0.0337 -7.13 (-13.7, -0.6)	<0.0001 -17.60 (-24.2, -11.0)	0.0020 -10.46 (-17.1, -3.9)
Week 76	60 5.5 (7.1) 0.5 (2.09)	57 9.0 (13.6) 7.0 (2.12)	46 14.6 (18.1) 16.6 (2.29)	0.0322 -6.53 (-12.5, -0.6)	<0.0001 -16.13 (-22.3, -9.9)	0.0031 -9.59 (-15.8, -3.4)
Week 91	57 5.8 (9.8) 1.9 (2.75)	52 10.3 (16.8) 10.6 (2.83)	38 15.9 (21.7) 23.5 (3.18)	0.0328 -8.66 (-16.6, -0.7)	<0.0001 -21.64 (-30.1, -13.2)	0.0035 -12.98 (-21.5, -4.5)
Final on therapy[b]	63 6.9 (10.8) 1.8 (2.74)	65 16.7 (21.7) 11.5 (2.71)	65 30.7 (28.4) 25.6 (2.71)	0.0124 -9.71 (-17.3, -2.1)	<0.0001 -23.83 (-31.4, -16.2)	0.0003 -14.12 (-21.7, -6.5)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error.
a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.
b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Change From Baseline in Subject Global Assessment of Disease Activity:

Part 1:

The mean change from baseline in the Subject's Global Assessment of Disease Activity score was statistically significant at all time points (Table 22). At Week 52, the mean (SD) change from baseline in the subject global assessment of disease activity score was -48.6 (26.2). The mean (SD) change from baseline in the subject global assessment of disease activity score at the final on-therapy visit was -42.8 (28.4).

Part 2:

The mean increase in the Subject's Global Assessment of Disease Activity score from the Part 2 baseline (ie, Week 52) was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at Week 64, Week 76, Week 91, and at the final on-therapy visit, and compared with the MTX group at Week 64 and at the final on-therapy visit (Table 23).

Table 22. Change From Baseline in Subject Global Assessment of Disease Activity Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	P-Value[a]
Baseline	N	306		-
	Mean	58.9		-
	SD	23.6		-
	Minimum	0.0		-
	Maximum	99.0		-
	Median	63.0		-
Week 2	N	301	301	-
	Mean	35.5	-23.4	<0.0001
	SD	23.4	24.4	-
	Minimum	0.0	-97.0	-
	Maximum	99.0	68.0	-
	Median	31.0	-20.0	-
Week 4	N	299	299	-
	Mean	31.3	-27.4	<0.0001
	SD	23.8	26.2	-
	Minimum	0.0	-94.0	-
	Maximum	100.0	44.0	-
	Median	25.0	-25.0	-
Week 8	N	294	294	-
	Mean	27.2	-31.8	<0.0001
	SD	22.6	26.0	-
	Minimum	0.0	-99.0	-
	Maximum	100.0	30.0	-
	Median	19.0	-30.0	-
Week 13	N	285	285	-
	Mean	24.3	-34.6	<0.0001
	SD	22.2	26.8	-
	Minimum	0.0	-99.0	-
	Maximum	99.0	51.0	-
	Median	17.0	-37.0	-
Week 26	N	277	277	-
	Mean	18.5	-40.1	<0.0001
	SD	20.6	28.1	-
	Minimum	0.0	-99.0	-
	Maximum	100.0	63.0	-
	Median	10.0	-41.0	-
Week 39	N	260	260	-
	Mean	13.5	-44.8	<0.0001
	SD	18.1	26.6	-
	Minimum	0.0	-99.0	-
	Maximum	100.0	29.0	-
	Median	6.0	-47.0	-
Week 52	N	223	223	-
	Mean	8.6	-48.6	<0.0001
	SD	13.5	26.2	-
	Minimum	0.0	-99.0	-
	Maximum	100.0	65.0	-
	Median	4.0	-50.0	-
Final on therapy visit	N	305	305	-

Table 22. Change From Baseline in Subject Global Assessment of Disease Activity Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	P-Value[a]
	Mean	16.3	-42.8	<0.0001
	SD	21.9	28.4	-
	Minimum	0.0	-99.0	-
	Maximum	100.0	65.0	-
	Median	7.0	-45.0	-

ETN=etanercept; MTX=methotrexate; N=number of subjects in the treatment group (ETN 50 mg+MTX) in each visit; SD=standard deviation

a. Paired t-test.

Table 23. Subject's Global Assessment of Disease Activity: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**PBO** **n** **Raw Mean (SD)** **Adj Change (SE)**	**E25 vs MTX** **p-Value** **Diff (95% CI)**	**E25 vs PBO** **p-Value** **Diff (95% CI)**	**MTX vs PBO** **p-Value** **Diff (95% CI)**
Week 52[a]	63 5.8 (6.3)	65 5.7 (7.7)	65 9.3 (14.1)	0.9402	0.0491	0.0397
Week 56	63 10.3 (14.8) 4.1 (2.15)	65 9.7 (16.3) 3.6 (2.11)	65 17.3 (22.1) 9.3 (2.13)	0.8494 0.57 (-5.4, 6.5)	0.0904 -5.16 (-11.1, 0.8)	0.0583 -5.73 (-11.7, 0.2)
Week 64	62 7.6 (9.1) 1.5 (3.00)	63 17.8 (25.5) 12.5 (2.97)	62 31.0 (31.4) 23.9 (3.01)	0.0101 -10.98 (-19.3, -2.7)	<0.0001 -22.35 (-30.7, -14.0)	0.0080 -11.36 (-19.7, -3.0)
Week 76	60 8.9 (12.1) 2.9 (2.25)	56 11.7 (17.9) 7.9 (2.30)	46 18.3 (18.7) 16.9 (2.50)	0.1216 -5.02 (-11.4, 1.4)	<0.0001 -13.98 (-20.7, -7.3)	0.0098 -8.95 (-15.7, -2.2)
Week 91	56 9.6 (14.1) 4.3 (2.60)	52 12.3 (17.5) 8.6 (2.69)	38 18.8 (25.7) 17.5 (3.13)	0.2473 -4.36 (-11.8, 3.1)	0.0016 -13.19 (-21.3, -5.1)	0.0348 -8.83 (-17.0, -0.6)
Final on therapy[b]	63 11.1 (16.2) 4.6 (3.32)	65 20.7 (25.9) 14.2 (3.27)	65 37.1 (33.9) 29.4 (3.30)	0.0397 -9.64 (-18.8, -0.5)	<0.0001 -24.84 (-34.1, -15.6)	0.0013 -15.21 (-24.4, -6.0)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in specific criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values are based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Change From Baseline in Subject Global Assessment of Pain:

Part 1:

The mean change from baseline in the Subject's Global Assessment of Pain score ([VAS] 100-mm) was statistically significant at all time points (Table 24). At Week 52, the mean (SD) change from baseline in the subject global assessment of pain score was -48.7 (24.4). The mean (SD) change from baseline in the subject global assessment of pain score at the final on-therapy visit was -42.4 (27.2).

Part 2:

The mean increase in the Subject's Global Assessment of Pain score from the Part 2 baseline (ie, Week 52) was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at all post-Week 52 time points, and compared with the MTX group at Week 64 and at the final on-therapy visit (Table 25).

Table 24. Change From Baseline in Subject Global Assessment of Pain (VAS) - Part 1

Visit	Statistic	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	306	-	-
	Mean	59.7	-	-
	SD	22.3	-	-
	Minimum	1.0	-	-
	Maximum	100.0	-	-
	Median	63.0	-	-
Week 2	N	301	301	-
	Mean	36.4	-23.2	<0.0001
	SD	23.1	23.8	-
	Minimum	0.0	-94.0	-
	Maximum	99.0	33.0	-
	Median	32.0	-18.0	-
Week 4	N	299	299	-
	Mean	32.1	-27.4	<0.0001
	SD	23.8	25.9	-
	Minimum	0.0	-89.0	-
	Maximum	99.0	41.0	-
	Median	26.0	-25.0	-
Week 8	N	294	294	-
	Mean	27.1	-32.6	<0.0001
	SD	22.7	25.7	-
	Minimum	0.0	-96.0	-
	Maximum	100.0	39.0	-
	Median	20.5	-32.0	-
Week 13	N	285	285	-
	Mean	24.2	-35.5	<0.0001
	SD	22.1	25.7	-
	Minimum	0.0	-96.0	-
	Maximum	99.0	53.0	-
	Median	18.0	-37.0	-
Week 26	N	277	277	-
	Mean	19.4	-40.1	<0.0001
	SD	21.3	27.1	-
	Minimum	0.0	-96.0	-
	Maximum	100.0	40.0	-
	Median	12.0	-41.0	-
Week 39	N	260	260	-
	Mean	14.0	-45.2	<0.0001
	SD	17.2	25.3	-
	Minimum	0.0	-96.0	-
	Maximum	100.0	16.0	-
	Median	8.0	-45.0	-
Week 52	N	223	223	-
	Mean	9.8	-48.7	<0.0001
	SD	13.8	24.4	-
	Minimum	0.0	-96.0	-
	Maximum	93.0	56.0	-
	Median	5.0	-50.0	-
Final on therapy visit	N	305	305	-

Table 24. Change From Baseline in Subject Global Assessment of Pain (VAS) - Part 1

Visit	Statistic	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
	Mean	17.4	-42.4	<0.0001
	SD	22.2	27.2	-
	Minimum	0.0	-96.0	-
	Maximum	100.0	56.0	-
	Median	9.0	-44.0	-

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation; VAS = visual analog scale.
a. Paired t-test.

Table 25. Subject's Global Assessment of Pain (VAS): Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**PBO** **n** **Raw Mean (SD)** **Adj Change (SE)**	**E25 vs MTX** **p-Value** **Diff (95% CI)**	**E25 vs PBO** **p-Value** **Diff (95% CI)**	**MTX vs PBO** **p-Value** **Diff (95% CI)**
Week 52[a]	63 7.3 (7.7)	65 6.9 (8.6)	65 9.9 (14.8)	0.7996	0.1865	0.1130
Week 56	63 10.9 (15.0) 3.4 (2.17)	65 10.2 (16.9) 2.9 (2.14)	65 18.8 (23.1) 9.7 (2.15)	0.8880 0.43 (-5.6, 6.4)	0.0381 -6.38 (-12.4, -0.4)	0.0260 -6.81 (-12.8, -0.8)
Week 64	62 8.0 (9.8) 0.7 (2.95)	63 18.0 (25.1) 11.7 (2.92)	62 31.7 (31.3) 23.7 (2.95)	0.0085 -11.04 (-19.2, -2.9)	<0.0001 -23.00 (-31.2, -14.8)	0.0045 -11.96 (-20.2, -3.8)
Week 76	60 9.8 (12.9) 2.6 (2.34)	56 12.3 (19.2) 8.0 (2.39)	46 17.6 (18.1) 16.7 (2.57)	0.1114 -5.38 (-12.0, 1.3)	0.0001 -14.08 (-21.0, -7.2)	0.0149 -8.70 (-15.7, -1.7)
Week 91	57 9.5 (12.7) 2.9 (2.47)	52 13.3 (16.4) 8.4 (2.57)	38 19.7 (26.1) 17.1 (2.99)	0.1248 -5.51 (-12.6, 1.6)	0.0004 -14.14 (-21.8, -6.5)	0.0306 -8.63 (-16.4, -0.8)
Final on therapy[b]	63 11.4 (15.4) 3.6 (3.21)	65 21.4 (24.8) 13.9 (3.17)	65 37.8 (33.7) 29.0 (3.18)	0.0239 -10.27 (-19.2, -1.4)	<0.0001 -25.43 (-34.4, -16.5)	0.0009 -15.17 (-24.0, -6.3)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in specific criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error; VAS = visual analog scale.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Patient Acceptable Symptom State:

Part 1:

The proportion of subjects who had a PASS at each time point during the study was statistically significantly greater than the proportion of subjects who had a PASS at baseline (Table 26). At Week 52, the proportion of subjects with a PASS was 93.6% (95% CI: 89.6, 96.5) vs 24.8% (95% CI: 20.1, 30.1) at baseline. The proportion of subjects with a PASS at their final on-therapy visit was 82.0% (95% CI: 77.2, 86.1).

Part 2:

A statistically significantly greater proportion of subjects in the E25+MTX treatment group had a PASS compared with the PBO group at Week 64, Week 76, and at the final on-therapy visit, and compared with the MTX group at Week 64 and Week 76 (Table 27).

Table 26. Proportion of Subjects Achieving a Patient Acceptable Symptom State - Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	p-Value[a]
Baseline	75/302	24.8% (20.1, 30.1)	
Week 2	151/297	50.8% (45.0, 56.7)	<0.0001
Week 4	180/292	61.6% (55.8, 67.2)	<0.0001
Week 8	189/288	65.6% (59.8, 71.1)	<0.0001
Week 13	197/279	70.6% (64.9, 75.9)	<0.0001
Week 26	213/268	79.5% (74.1, 84.1)	<0.0001
Week 39	219/257	85.2% (80.3, 89.3)	<0.0001
Week 52	206/220	93.6% (89.6, 96.5)	<0.0001
Final on therapy visit	250/305	82.0% (77.2, 86.1)	<0.0001

CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group (ETN 50 mg+MTX); n = number of subjects in each criteria.
a. P-value is from McNemar's test for no change from baseline in response rate.

Table 27. Number (%) of Subjects With a Patient Acceptable Symptom State, mITT Population – Part 2

	Treatment Group			Pairwise Comparison[a]		
Time Point	E25+MTX n/N (%) 95% CI	MTX n/N (%) 95% CI	PBO n/N (%) 95% CI	E25 vs MTX p-Value OR (95% CI)	E25 vs PBO p-Value OR (95% CI)	MTX vs PBO p-Value OR (95% CI)
Week 52[b]	57/61 (93.4) 84.1, 98.2	64/65 (98.5) 91.7, 100	61/64 (95.3) 86.9, 99.0	0.1848 NE	0.6509 NE	0.3264 NE
Week 56	57/63 (90.5) 80.4, 96.4	58/63 (92.1) 82.4, 97.4	53/64 (82.8) 71.3, 91.1	0.6906 0.77 (0.2, 2.8)	0.1892 2.03 (0.7, 5.8)	0.1010 2.63 (0.8, 8.4)
Week 64	58/61 (95.1) 86.3, 99.0	51/60 (85.0) 73.4, 92.9	42/60 (70.0) 56.8, 81.2	0.0442 3.99 (1.0, 15.3)	0.0008 9.01 (2.5, 32.6)	0.0624 2.26 (1.0, 5.3)
Week 76	57/60 (95.0) 86.1, 99.0	48/56 (85.7) 73.8, 93.6	38/45 (84.4) 70.5, 93.5	0.0299 4.33 (1.2, 16.2)	0.0041 6.52 (1.8, 23.5)	0.3472 1.51 (0.6, 3.5)
Week 91	52/57 (91.2) 80.7, 97.1	46/52 (88.5) 76.6, 95.6	33/38 (86.8) 71.9, 95.6	0.4717 1.51 (0.5, 4.6)	0.0551 2.77 (1.0, 7.8)	0.2141 1.84 (0.7, 4.8)
Final on therapy[b]	56/63 (88.9) 78.4, 95.4	50/65 (76.9) 64.8, 86.5	38/65 (58.5) 45.6, 70.6	0.0784 2.40 (0.9, 6.4)	0.0002 5.68 (2.2, 14.4)	0.0260 2.37 (1.1, 5.1)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept+methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; NE = not estimable; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group).

a. Odds ratios and p-values for pairwise treatment comparisons at Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for treatment, visit, and interaction of treatment and visit.

b. Baseline and final on-therapy comparisons were based on a model with treatment only.

ACR 20 Responses:

Part 1:

The proportion of subjects who achieved an ACR 20 response was statistically significantly different from 0 at all time points (Table 28). At Week 52, the proportion of subjects with an ACR 20 response was 95.9% (95% CI: 92.4, 98.1). The proportion of subjects with an ACR 20 response at their final on-therapy visit was 85.7% (95% CI: 81.2, 89.5).

Table 28. Proportion of Subjects Achieving an ACR 20 Response in Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-value[a]
Week 2	139/297	46.8% (41.0, 52.7)	<0.0001
Week 4	195/295	66.1% (60.4, 71.5)	<0.0001
Week 8	225/290	77.6% (72.3, 82.3)	<0.0001
Week 13	232/280	82.9% (77.9, 87.1)	<0.0001
Week 26	232/272	85.3% (80.5, 89.3)	<0.0001
Week 39	235/256	91.8% (87.7, 94.9)	<0.0001
Week 52	212/221	95.9% (92.4, 98.1)	<0.0001
Final on therapy visit	258/301	85.7% (81.2, 89.5)	<0.0001

ACR 20 = American College of Rheumatology's definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures; CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n=number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion was significantly different from 0.

ACR 50 Responses:

The proportion of subjects who achieved an ACR 50 response was statistically significantly different from 0 at all time points (Table 29). At Week 52, the proportion of subjects with an ACR 50 response was 91.4% (95% CI: 86.9, 94.7). The proportion of subjects with an ACR 50 response at their final on-therapy visit was 76.1% (95% CI: 70.9, 80.8).

Table 29. Proportion of Subjects Achieving an ACR 50 Response in Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-value[a]
Week 2	52/297	17.5% (13.4, 22.3)	<0.0001
Week 4	114/295	38.6% (33.1, 44.5)	<0.0001
Week 8	144/290	49.7% (43.8, 55.6)	<0.0001
Week 13	169/280	60.4% (54.4, 66.1)	<0.0001
Week 26	190/272	69.9% (64.0, 75.2)	<0.0001
Week 39	218/256	85.2% (80.2, 89.3)	<0.0001
Week 52	202/221	91.4% (86.9, 94.7)	<0.0001
Final on therapy visit	229/301	76.1% (70.9, 80.8)	<0.0001

ACR 50 = American College of Rheumatology's definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures; CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion was significantly different from 0.

ACR 70 Responses:

The proportion of subjects who achieved an ACR 70 response was statistically significantly different from 0 at all time points (Table 30). At Week 52, the proportion of subjects with an ACR 70 response was 79.6% (95% CI: 73.7, 84.7). The proportion of subjects with an ACR 70 response at their final on-therapy visit was 65.8% (95% CI: 60.1, 71.1).

Table 30. Proportion of Subjects Achieving an ACR 70 Response in Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-Value[a]
Week 2	17/297	5.7% (3.4, 9.0)	<0.0001
Week 4	49/295	16.6% (12.5, 21.4)	<0.0001
Week 8	80/290	27.6% (22.5, 33.1)	<0.0001
Week 13	115/280	41.1% (35.3, 47.1)	<0.0001
Week 26	146/272	53.7% (47.6, 59.7)	<0.0001
Week 39	178/256	69.5% (63.5, 75.1)	<0.0001
Week 52	176/221	79.6% (73.7, 84.7)	<0.0001
Final on therapy visit	198/301	65.8% (60.1, 71.1)	<0.0001

ACR 70 = American College of Rheumatology's definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures; CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion was significantly different from 0.

ACR 90 Responses:

The proportion of subjects who achieved an ACR 90 response was statistically significantly different from 0 at all time points (Table 31). At Week 52, the proportion of subjects with an ACR 90 response was 43.9% (95% CI: 37.2, 50.7). The proportion of subjects with an ACR 90 response at their final on-therapy visit was 34.9% (95% CI: 29.5, 40.6).

Table 31. Proportion of Subjects Achieving an ACR 90 Response in Part 1

Week	ETN 50 mg/MTX n/N	Proportion (Exact 95% CI)[a]	Exact p-Value[a]
Week 2	2/297	0.7% (0.1, 2.4)	<0.0001
Week 4	11/295	3.7% (1.9, 6.6)	<0.0001
Week 8	22/290	7.6% (4.8, 11.3)	<0.0001
Week 13	34/280	12.1% (8.6, 16.6)	<0.0001
Week 26	70/272	25.7% (20.6, 31.4)	<0.0001
Week 39	85/256	33.2% (27.5, 39.3)	<0.0001
Week 52	97/221	43.9% (37.2, 50.7)	<0.0001
Final on therapy visit	105/301	34.9% (29.5, 40.6)	<0.0001

ACR 90 = American College of Rheumatology's definition for calculating improvement in rheumatoid arthritis; calculated as a ≥90% improvement in tender and swollen joint counts and ≥90% improvement in 3 of the 5 remaining ACR core set measures; CI = confidence interval; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group; n = number of subjects in each criteria.
a. Binomial test-value tests the null hypothesis that the proportion was significantly different from 0.

Part 2: Table 32 presents ACR responses (20, 50, 70 and 90) using Part 1 Baseline, mITT Population.

Table 32. Number (%) of Subjects With ACR Response Using Part 1 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX p-Value OR (95% CI)**	**E25 vs PBO p-Value OR (95% CI)**	**MTX vs PBO p-Value OR (95% CI)**
ACR 20 Response						
Week 52[b]	61/63 (96.8) 89.0, 99.6	63/63 (100) 94.3, 100	64/65 (98.5) 91.7, 100	0.9999 NE	0.5493 NE	0.9999 NE
Week 56	59/63 (93.7) 84.5, 98.2	59/63 (93.7) 84.5, 98.2	56/63 (88.9) 78.4, 95.4	1.0000 1.00 (0.2, 4.2)	0.3354 1.87 (0.5, 6.7)	0.3354 1.87 (0.5, 6.7)
Week 64	61/62 (98.4) 91.3, 100	51/61 (83.6) 71.9, 91.8	44/62 (71.0) 58.1, 81.8	0.0098 11.43 (1.8, 72.6)	0.0007 22.88 (3.7, 140.3)	0.1065 2.00 (0.9, 4.6)
Week 76	57/60 (95.0) 86.1, 99.0	51/55 (92.7) 82.4, 98.0	40/46 (87.0) 73.7, 95.1	0.3388 1.97 (0.5, 7.9)	0.0245 4.45 (1.2, 16.4)	0.1237 2.26 (0.8, 6.4)
Week 91	55/57 (96.5) 87.9, 99.6	48/50 (96.0) 86.3, 99.5	31/38 (81.6) 65.7, 92.3	0.4075 1.83 (0.4, 7.6)	0.0011 8.88 (2.4, 33.1)	0.0031 4.87 (1.7, 13.9)
Final on therapy[b]	58/63 (92.1) 82.4, 97.4	52/63 (82.5) 70.9, 90.9	37/65 (56.9) 44.0, 69.2	0.1167 2.45 (0.8, 7.5)	<0.0001 8.78 (3.1, 24.8)	0.0022 3.58 (1.6, 8.1)
ACR 50 Response						
Week 52[b]	58/63 (92.1) 82.4, 97.4	61/63 (96.8) 89.0, 99.6	62/65 (95.4) 87.1, 99.0	0.2590 NE	0.4430 NE	0.6758 NE
Week 56	55/63 (87.3) 76.5, 94.4	58/63 (92.1) 82.4, 97.4	48/63 (76.2) 63.8, 86.0	0.3836 0.59 (0.2, 1.9)	0.1079 2.16 (0.8, 5.5)	0.0189 3.65 (1.2, 10.7)
Week 64	59/62 (95.2) 86.5, 99.0	47/61 (77.0) 64.5, 86.8	33/62 (53.2) 40.1, 66.0	0.0047 5.99 (1.7, 20.7)	<0.0001 16.79 (5.0, 56.1)	0.0082 2.80 (1.3, 6.0)
Week 76	54/60 (90.0) 79.5, 96.2	48/55 (87.3) 75.5, 94.7	33/46 (71.7) 56.5, 84.0	0.2960 1.76 (0.6, 5.0)	0.0015 4.96 (1.8, 13.3)	0.0174 2.83 (1.2, 6.7)
Week 91	48/57 (84.2) 72.1, 92.5	45/50 (90.0) 78.2, 96.7	29/38 (76.3) 59.8, 88.6	0.5951 0.77 (0.3, 2.0)	0.0934 2.19 (0.9, 5.5)	0.0314 2.85 (1.1, 7.4)
Final on therapy[b]	50/63 (79.4) 67.3, 88.5	47/63 (74.6) 62.1, 84.7	32/65 (49.2) 36.6, 61.9	0.5261 1.31 (0.6, 3.0)	0.0005 3.97 (1.8, 8.7)	0.0036 3.03 (1.4, 6.4)

Table 32. Number (%) of Subjects With ACR Response Using Part 1 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX p-Value OR (95% CI)**	**E25 vs PBO p-Value OR (95% CI)**	**MTX vs PBO p-Value OR (95% CI)**
ACR 70 Response						
Week 52[b]	52/63 (82.5) 70.9, 90.9	56/63 (88.9) 78.4, 95.4	52/65 (80.0) 68.2, 88.9	0.3121 NE	0.7130 NE	0.1714 NE
Week 56	46/63 (73.0) 60.3, 83.4	51/63 (81.0) 69.1, 89.8	37/63 (58.7) 45.6, 71.0	0.2919 0.64 (0.3, 1.5)	0.0787 1.95 (0.9, 4.1)	0.0061 3.07 (1.4, 6.8)
Week 64	49/62 (79.0) 66.8, 88.3	42/61 (68.9) 55.7, 80.1	24/62 (38.7) 26.6, 51.9	0.1638 1.77 (0.8, 4.0)	<0.0001 6.12 (2.8, 13.5)	0.0011 3.46 (1.6, 7.3)
Week 76	47/60 (78.3) 65.8, 87.9	41/55 (74.5) 61.0, 85.3	25/46 (54.3) 39.0, 69.1	0.2870 1.56 (0.7, 3.5)	0.0008 4.10 (1.8, 9.3)	0.0159 2.62 (1.2, 5.7)
Week 91	44/57 (77.2) 64.2, 87.3	39/50 (78.0) 64.0, 88.5	25/38 (65.8) 48.6, 80.4	0.6152 1.23 (0.5, 2.8)	0.0432 2.36 (1.0, 5.4)	0.1189 1.91 (0.8, 4.3)
Final on therapy[b]	46/63 (73.0) 60.3, 83.4	39/63 (61.9) 48.8, 73.9	26/65 (40.0) 28.0, 52.9	0.1848 1.67 (0.8, 3.5)	0.0002 4.06 (1.9, 8.6)	0.0140 2.44 (1.2, 5.0)
ACR 90 Response						
Week 52[b]	32/63 (50.8) 37.9, 63.6	31/63 (49.2) 36.4, 62.1	25/65 (38.5) 26.7, 51.4	0.8586 NE	0.1616 NE	0.2215 NE
Week 56	32/63 (50.8) 37.9, 63.6	31/63 (49.2) 36.4, 62.1	20/63 (31.7) 20.6, 44.7	0.8586 1.07 (0.5, 2.1)	0.0264 2.27 (1.1, 4.7)	0.0405 2.13 (1.0, 4.4)
Week 64	29/62 (46.8) 34.0, 59.9	22/61 (36.1) 24.2, 49.4	11/62 (17.7) 9.2, 29.5	0.2082 1.59 (0.8, 3.3)	0.0007 4.22 (1.8, 9.7)	0.0244 2.65 (1.1, 6.2)
Week 76	25/60 (41.7) 29.1, 55.1	18/55 (32.7) 20.7, 46.7	13/46 (28.3) 16.0, 43.5	0.2012 1.65 (0.8, 3.6)	0.0446 2.39 (1.0, 5.6)	0.4147 1.45 (0.6, 3.5)
Week 91	30/57 (52.6) 39.0, 66.0	19/50 (38.0) 24.7, 52.8	12/38 (31.6) 17.5, 48.7	0.0535 2.15 (1.0, 4.7)	0.0064 3.22 (1.4, 7.5)	0.3696 1.50 (0.6, 3.6)
Final on therapy[b]	31/63 (49.2) 36.4, 62.1	19/63 (30.2) 19.2, 43.0	12/65 (18.5) 9.9, 30.0	0.0301 2.24 (1.1, 4.7)	0.0004 4.28 (1.9, 9.5)	0.1255 1.91 (0.8, 4.4)

Table 32. Number (%) of Subjects With ACR Response Using Part 1 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX p-Value OR (95% CI)**	**E25 vs PBO p-Value OR (95% CI)**	**MTX vs PBO p-Value OR (95% CI)**

ACR = American College of Rheumatology; ACR 20/50/70/90 response=≥20%/50%/70%/90% improvement in tender and swollen joint counts and ≥20%/50%/70%/90% improvement in 3 of the 5 remaining ACR core set measures; CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX=placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; NE = not estimable; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group).

a. Odds ratios and p-values for pairwise treatment comparisons at Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for treatment, visit, and interaction of treatment and visit.
b. Baseline and final on-therapy comparisons were based on a model with treatment only.

Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis:

Part 1:

The mean change from baseline in WPAI: RA percent 'work time missed due to problem' was statistically significant at all time points (Table 33). At Week 52, the mean (SD) change from baseline in WPAI: RA 'work time missed due to problem' was -12.9% (32.4). The mean (SD) change from baseline in WPAI: RA 'work time missed due to problem' at the final on-therapy visit was -10.7% (35.3). Table 34 presents the mean change from baseline in WPAI: RA percent 'impairment while working due to problem' which was statistically significant at all time points. Table 35 presents the mean change from baseline in WPAI: RA percent 'overall work impairment due to problem' was statistically significant at all time points. Table 36 presents the mean change from baseline in WPAI: RA percent 'activity impairment due to problem' was statistically significant at all time points.

Part 2:

Table 37 presents the proportions of subjects in the E25+MTX and PBO treatment groups who were employed were not significantly different at any time point. Table 38 presents the differences in mean change in percent work time missed in the past 7 days from the Part 2 baseline (ie, Week 52) were not statistically significant for any pairwise comparison at any time point. Table 39 presents the mean increase from the Part 2 baseline (ie, Week 52) in percent impairment while working in the past 7 days which was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at all post-Week 52 time points, and compared with the MTX group at Week 64 and at the final on-therapy visit. Table 40 presents the mean increase from the Part 2 baseline in percent overall work impairment in the past 7 days in the E25+MTX treatment group compared with the MTX group which was not statistically significant at any post-Week 52 time point. Table 41 reports the mean increase from the Part 2 baseline (ie, Week 52) in percent activity impairment in the past 7 days was statistically significantly smaller in the E25+MTX treatment group compared with the PBO group at all post-Week 52 time points, and compared with the MTX group at Week 64, Week 91, and at the final on-therapy visit.

Table 33. Change From Baseline in WPAI: RA Percent Work Time Missed Due to Problem – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	157		
	Mean	19.8		
	SD	36.0		
	Minimum	0.0		
	Maximum	100.0		
	Median	0.0		
Week 13	N	147	116	
	Mean	6.6	-8.9	0.0063
	SD	20.1	34.5	
	Minimum	0.0	-100.0	
	Maximum	100.0	100.0	
	Median	0.0	0.0	
Week 26	N	150	110	
	Mean	6.8	-8.8	0.0053
	SD	21.9	32.5	
	Minimum	0.0	-100.0	
	Maximum	100.0	100.0	
	Median	0.0	0.0	
Week 39	N	147	110	
	Mean	4.5	-9.0	0.0027
	SD	18.8	30.7	
	Minimum	0.0	-100.0	
	Maximum	100.0	100.0	
	Median	0.0	0.0	
Week 52	N	115	93	
	Mean	1.2	-12.9	0.0002
	SD	9.5	32.4	
	Minimum	0.0	-100.0	
	Maximum	100.0	100.0	
	Median	0.0	0.0	
Final on therapy visit	N	190	138	
	Mean	7.1	-10.7	0.0005
	SD	23.6	35.3	
	Minimum	0.0	-100.0	
	Maximum	100.0	100.0	
	Median	0.0	0.0	

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Paired t-test.

Table 34. Change From Baseline in WPAI: RA Percent Impairment While Working Due to Problem – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	189		
	Mean	49.4		
	SD	27.8		
	Minimum	0.0		
	Maximum	100.0		
	Median	50.0		
Week 13	N	183	140	
	Mean	23.1	-27.1	<0.0001
	SD	23.1	27.8	
	Minimum	0.0	-100.0	
	Maximum	100.0	40.0	
	Median	20.0	-25.0	
Week 26	N	179	138	
	Mean	18.3	-31.5	<0.0001
	SD	21.8	28.0	
	Minimum	0.0	-100.0	
	Maximum	100.0	20.0	
	Median	10.0	-30.0	
Week 39	N	165	129	
	Mean	13.2	-35.3	<0.0001
	SD	17.9	27.3	
	Minimum	0.0	-100.0	
	Maximum	100.0	20.0	
	Median	10.0	-30.0	
Week 52	N	149	116	
	Mean	11.1	-36.6	<0.0001
	SD	17.2	31.5	
	Minimum	0.0	-100.0	
	Maximum	100.0	60.0	
	Median	10.0	-30.0	
Final on therapy visit	N	243	169	
	Mean	18.4	-33.8	<0.0001
	SD	24.0	30.3	
	Minimum	0.0	-100.0	
	Maximum	100.0	60.0	
	Median	10.0	-30.0	

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Paired t-test.

Table 35. Change From Baseline in WPAI: RA Percent Overall Work Impairment due to Problem – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	140		
	Mean	50.1		
	SD	29.1		
	Minimum	0.0		
	Maximum	100.0		
	Median	50.0		
Week 13	N	139	100	
	Mean	22.1	-27.6	<0.0001
	SD	23.2	27.4	
	Minimum	0.0	-100.0	
	Maximum	100.0	30.0	
	Median	10.0	-27.8	
Week 26	N	139	94	
	Mean	18.5	-32.2	<0.0001
	SD	24.5	28.0	
	Minimum	0.0	-100.0	
	Maximum	100.0	20.0	
	Median	10.0	-30.0	
Week 39	N	139	97	
	Mean	12.0	-35.9	<0.0001
	SD	17.8	27.0	
	Minimum	0.0	-100.0	
	Maximum	92.2	10.0	
	Median	10.0	-30.0	
Week 52	N	111	81	
	Mean	9.3	-37.3	<0.0001
	SD	17.0	30.7	
	Minimum	0.0	-100.0	
	Maximum	100.0	40.0	
	Median	0.0	-31.0	
Final on therapy visit	N	187	124	
	Mean	16.6	-35.5	<0.0001
	SD	25.9	31.3	
	Minimum	0.0	-100.0	
	Maximum	100.0	40.0	
	Median	10.0	-30.5	

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Paired t-test.

Table 36. Change From Baseline in WPAI: RA Percent Activity Impairment due to Problem – Part 1

Visit	Statistic	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	282		
	Mean	57.2		
	SD	24.3		
	Minimum	0.0		
	Maximum	100.0		
	Median	60.0		
Week 13	N	259	244	
	Mean	27.2	-30.3	<0.0001
	SD	23.9	26.0	
	Minimum	0.0	-100.0	
	Maximum	90.0	50.0	
	Median	20.0	-30.0	
Week 26	N	256	241	
	Mean	22.1	-34.7	<0.0001
	SD	23.9	27.5	
	Minimum	0.0	-100.0	
	Maximum	100.0	30.0	
	Median	20.0	-30.0	
Week 39	N	240	224	
	Mean	16.5	-39.9	<0.0001
	SD	19.8	27.0	
	Minimum	0.0	-100.0	
	Maximum	100.0	20.0	
	Median	10.0	-40.0	
Week 52	N	204	194	
	Mean	13.0	-41.3	<0.0001
	SD	17.4	28.6	
	Minimum	0.0	-100.0	
	Maximum	100.0	50.0	
	Median	10.0	-40.0	
Final on therapy visit	N	290	270	
	Mean	21.5	-36.4	<0.0001
	SD	25.5	29.4	
	Minimum	0.0	-100.0	
	Maximum	100.0	50.0	
	Median	10.0	-40.0	

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Paired t-test.

Table 37. WPAI: RA: Number (%) of Subjects who Were Employed (Working for Pay), mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX p-Value OR (95% CI)**	**E25 vs PBO p-Value OR (95% CI)**	**MTX vs PBO p-Value OR (95% CI)**
Week 52[b]	36/57 (63.2) 49.3, 75.6	49/64 (76.6) 64.3, 86.2	32/63 (50.8) 37.9, 63.6	0.1097 NE	0.1735 NE	0.0030 NE
Week 64	34/57 (59.6) 45.8, 72.4	47/63 (74.6) 62.1, 84.7	29/58 (50.0) 36.6, 63.4	0.0551 0.47 (0.2, 1.0)	0.3346 1.43 (0.7, 2.9)	0.0043 3.02 (1.4, 6.4)
Week 76	34/58 (58.6) 44.9, 71.4	41/56 (73.2) 59.7, 84.2	21/44 (47.7) 32.5, 63.3	0.0701 0.49 (0.2, 1.1)	0.2758 1.50 (0.7, 3.1)	0.0045 3.04 (1.4, 6.5)
Week 91	32/55 (58.2) 44.1, 71.3	38/51 (74.5) 60.4, 85.7	15/37 (40.5) 24.8, 57.9	0.0501 0.46 (0.2, 1.0)	0.2131 1.60 (0.8, 3.3)	0.0019 3.48 (1.6, 7.6)
Final on therapy[b]	34/60 (56.7) 43.2, 69.4	49/65 (75.4) 63.1, 85.2	31/64 (48.4) 35.8, 61.3	0.0284 0.43 (0.2, 0.9)	0.3597 1.39 (0.7, 2.8)	0.0019 3.26 (1.5, 6.9)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); N=number of subjects in the treatment group; n = number of subjects in each criteria; NE = not estimable; OR = odds ratio; PBO = placebo etanercept +placebo methotrexate (group); WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Odds ratios and p-values for pairwise treatment comparisons at Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for treatment, visit, and interaction of treatment and visit.

b. Baseline and final on-therapy comparisons were based on a model with treatment only.

Table 38. WPAI: RA--Percent Work Time Missed in the Past 7 Days due to Problem: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	E25+MTX n Raw Mean (SD) Adj Change (SE)	MTX n Raw Mean (SD) Adj Change (SE)	PBO n Raw Mean (SD) Adj Change (SE)	E25 vs MTX P-Value Diff (95% CI)	E25 vs PBO P-Value Diff (95% CI)	MTX vs PBO P-Value Diff (95% CI)
Week 52[a]	29 0.2 (1.2)	43 0.1 (0.6)	25 0.0 (0.0)	0.4830	0.2918	0.6342
Week 64	30 2.0 (9.2) 1.9 (2.78)	44 2.7 (15.2) 2.6 (2.29)	26 5.9 (19.7) 6.1 (3.04)	0.8328 -0.76 (-7.9, 6.4)	0.3115 -4.20 (-12.4, 4.0)	0.3698 -3.43 (-11.0, 4.1)
Week 76	28 0.0 (0.0) -0.1 (2.38)	33 3.0 (17.4) 2.9 (2.19)	18 2.9 (9.7) 2.6 (3.09)	0.3510 -3.03 (-9.5, 3.4)	0.4936 -2.70 (-10.5, 5.1)	0.9296 0.34 (-7.2, 7.9)
Week 91	29 4.5 (17.7) 4.4 (3.78)	32 4.3 (18.2) 4.0 (3.63)	14 7.1 (26.7) 7.0 (5.79)	0.9338 0.44 (-10.0, 10.9)	0.7130 -2.55 (-16.4, 11.2)	0.6628 -2.99 (-16.6, 10.6)
Final on therapy[b]	34 3.8 (16.4) 3.6 (3.65)	48 5.5 (20.5) 5.3 (3.07)	29 10.0 (26.2) 10.2 (4.06)	0.7181 -1.72 (-11.2, 7.7)	0.2299 -6.63 (-17.5, 4.3)	0.3386 -4.91 (-15.0, 5.2)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Table 39. WPAI: RA--Percent Impairment While Working in the Past 7 Days due to Problem: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**PBO** **n** **Raw Mean (SD)** **Adj Change (SE)**	**E25 vs MTX** **p-Value** **Diff (95% CI)**	**E25 vs PBO** **p-Value** **Diff (95% CI)**	**MTX vs PBO** **p-Value** **Diff (95% CI)**
Week 52[a]	37 6.2 (9.2)	54 8.9 (15.5)	36 14.2 (17.9)	0.3984	0.0232	0.0995
Week 64	37 6.2 (10.1) -2.5 (3.57)	49 18.2 (26.0) 9.6 (3.16)	31 30.0 (29.7) 18.2 (3.96)	0.0123 -12.13 (-21.6, -2.7)	0.0002 -20.72 (-31.3, -10.1)	0.0920 -8.60 (-18.6, 1.4)
Week 76	38 6.6 (9.1) -0.6 (2.16)	38 8.7 (14.0) 2.3 (2.01)	23 16.5 (13.4) 12.2 (2.54)	0.3355 -2.87 (-8.8, 3.0)	0.0003 -12.73 (-19.4, -6.0)	0.0030 -9.86 (-16.3, -3.4)
Week 91	37 9.5 (16.1) 1.8 (3.16)	35 12.6 (18.0) 8.6 (3.06)	18 23.9 (20.9) 18.4 (4.23)	0.1303 -6.74 (-15.5, 2.0)	0.0024 -16.59 (-27.1, -6.0)	0.0621 -9.85 (-20.2, 0.5)
Final on therapy[b]	45 10.4 (15.5) 1.1 (3.51)	54 21.3 (25.0) 11.1 (3.10)	40 31.3 (27.8) 19.9 (3.76)	0.0340 -10.01 (-19.3, -0.8)	0.0004 -18.83 (-29.1, -8.5)	0.0737 -8.82 (-18.5, 0.9)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Table 40. WPAI: RA--Percent Overall Work Impairment in the Past 7 Days due to Problem: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**PBO** **n** **Raw Mean (SD)** **Adj Change (SE)**	**E25 vs MTX** **p-Value** **Diff (95% CI)**	**E25 vs PBO** **p-Value** **Diff (95% CI)**	**MTX vs PBO** **p-Value** **Diff (95% CI)**
Week 52[a]	27 5.3 (9.8)	42 6.7 (15.0)	24 9.2 (12.8)	0.6682	0.3026	0.4720
Week 64	29 6.3 (11.5) 0.1 (4.49)	43 18.1 (28.0) 11.5 (3.75)	25 29.3 (29.3) 22.4 (5.01)	0.0530 -11.46 (-23.1, 0.2)	0.0013 -22.32 (-35.7, -8.9)	0.0857 -10.86 (-23.3, 1.6)
Week 76	27 5.2 (8.0) -0.9 (2.40)	30 8.0 (13.2) 2.6 (2.18)	18 19.8 (17.0) 16.6 (2.95)	0.2937 -3.45 (-9.9, 3.1)	<0.0001 -17.44 (-25.1, -9.8)	0.0003 -13.99 (-21.3, -6.7)
Week 91	28 11.0 (19.8) 5.4 (3.98)	30 12.5 (19.2) 9.5 (3.74)	13 20.0 (22.7) 22.0 (5.75)	0.4664 -4.01 (-15.0, 6.9)	0.0210 -16.57 (-30.6, -2.6)	0.0713 -12.56 (-26.2, 1.1)
Final on therapy[b]	34 10.9 (18.6) 4.4 (4.32)	48 20.7 (26.6) 13.3 (3.60)	28 32.1 (29.2) 25.1 (4.84)	0.1158 -8.92 (-20.1, 2.2)	0.0021 -20.64 (-33.6, -7.7)	0.0546 -11.72 (-23.7, 0.2)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE=standard error; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Table 41. WPAI: RA--Percent Activity Impairment in the Past 7 Days due to Problem: Between-Group Comparison of Change From Part 2 Baseline, mITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**MTX** **n** **Raw Mean (SD)** **Adj Change (SE)**	**PBO** **n** **Raw Mean (SD)** **Adj Change (SE)**	**E25 vs MTX** **P-Value** **Diff (95% CI)**	**E25 vs PBO** **P-Value** **Diff (95% CI)**	**MTX vs PBO** **P-Value** **Diff (95% CI)**
Week 52[a]	56 8.6 (11.0)	60 10.0 (15.9)	60 16.8 (20.0)	0.6356	0.0067	0.0220
Week 64	56 10.9 (13.2) -0.5 (3.21)	60 21.2 (28.8) 9.9 (3.10)	57 32.5 (29.1) 19.1 (3.18)	0.0201 -10.46 (-19.3, -1.7)	<0.0001 -19.69 (-28.6, -10.7)	0.0398 -9.22 (-18.0, -0.4)
Week 76	57 14.0 (24.7) 2.9 (2.94)	55 16.0 (20.4) 7.1 (2.96)	41 20.0 (17.3) 13.9 (3.35)	0.3098 -4.26 (-12.5, 4.0)	0.0149 -11.04 (-19.9, -2.2)	0.1319 -6.78 (-15.6, 2.1)
Week 91	53 8.5 (12.6) -1.8 (2.83)	49 14.5 (18.5) 7.3 (2.87)	37 23.8 (26.3) 17.9 (3.20)	0.0256 -9.11 (-17.1, -1.1)	<0.0001 -19.62 (-28.1, -11.1)	0.0161 -10.51 (-19.0, -2.0)
Final on therapy[b]	60 11.2 (15.4) -0.9 (3.24)	64 24.4 (26.8) 12.2 (3.13)	64 37.7 (30.4) 24.2 (3.16)	0.0040 -13.11 (-22.0, -4.2)	<0.0001 -25.05 (-34.0, -16.1)	0.0082 -11.95 (-20.8, -3.1)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX=placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); SD = standard deviation; SE = standard error; WPAI: RA = Work Productivity Activity Impairment Questionnaire: Rheumatoid Arthritis.

a. Adjusted means, mean differences (Diff), and p-values for pairwise treatment comparisons at the Week 56 to Week 91 visits were based on a longitudinal statistical model with factors for Week 52 value, treatment, visit, and interaction of treatment and Week 52 value and treatment and visit. Week 52 p-values were based on 1-way ANOVA only.

b. Final on-therapy comparisons were based on 1-way ANCOVA model adjusting for Week 52.

Modified Total Sharp Score:

Part 1:

Table 42 and Table 43 presents the mean change and annual rate of change from baseline in mTSS respectively.

Part 2:

Table 44 and Table 45 present proportion of subjects in the E25+MTX treatment group compared with the PBO and MTX groups who, at Week 91 or at the final on-therapy visit, had an mTSS change of ≤0.0 and mTSS change of ≤0.5 respectively from the Part 2 baseline which were not significantly different. Table 46 presents the differences in change from baseline in mTSS which were not statistically significant for any pairwise comparison at Week 91 or at the final on-therapy visit.

Table 42. Change From Baseline in Modified Total Sharp Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	269	-	-
	Mean	7.9	-	-
	SD	12.7	-	-
	Minimum	0.0	-	-
	Maximum	102.5	-	-
	Median	3.5	-	-
Week 52	N	200	200	-
	Mean	8.9	0.3	0.1183
	SD	14.0	3.0	-
	Minimum	0.0	-8.0	-
	Maximum	101.0	35.0	-
	Median	4.0	0.0	-

ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group in each visit; SD = standard deviation.
a. Paired t-test.

Table 43. Annual Rate of Change From Baseline in Modified Total Sharp Score – Part 1

Visit	Statistics	ETN 50 mg/MTX		
		Value at Visit	Change From Baseline	p-Value[a]
Baseline	N	269	-	-
	Mean	7.93	-	-
	SD	12.74	-	-
	Minimum	0.00	-	-
	Maximum	102.50	-	-
	Median	3.50	-	-
Week 52	N	200	200	-
	Mean	8.93	0.33	0.1235
	SD	14.05	3.04	-
	Minimum	0.00	-7.98	-
	Maximum	100.92	35.51	-
	Median	4.00	0.00	-
Final on therapy visit	N	269	269	-
	Mean	8.31	0.38	0.0286
	SD	13.05	2.86	-
	Minimum	0.00	-7.98	-
	Maximum	100.92	35.51	-
	Median	3.55	0.00	-

ETN=etanercept; MTX=methotrexate; N=number of subjects in the treatment group in each visit; SD=standard deviation.
a. Paired t-test.

Table 44. Number (%) of Subjects With a Modified Total Sharp Score Change From Part 2 Baseline ≤0.0, rITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX p-Value OR (95% CI)**	**E25 vs PBO p-Value OR (95% CI)**	**MTX vs PBO p-Value OR (95% CI)**
Week 91	44/51 (86.3)	42/45 (93.3)	24/30 (80.0)	0.2680	0.4598	0.0957
	73.7, 94.3	81.7, 98.6	7.7, 38.6	0.45 (0.1, 1.9)	1.57 (0.5, 5.2)	3.50 (0.8, 15.3)
Final on therapy[b]	48/58 (82.8)	52/56 (92.9)	41/49 (83.7)	0.1106	0.8997	0.1503
	70.6, 91.4	82.7, 98.0	70.3, 92.7	0.37 (0.1, 1.3)	0.94 (0.3, 2.6)	2.54 (0.7, 9.0)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; OR = odds ratio; PBO = placebo etanercept + placebo methotrexate (group); rITT = radiographic intent-to-treat.

a. Odds ratios and p-values for pairwise treatment comparisons at the Week 91 visit were based on a logistic regression statistical model with one factor (treatment).

b. Final on-therapy comparisons were based on a logistic regression model with treatment only as a factor in the model.

Table 45. Number (%) of Subjects With a Modified Total Sharp Score Change From Part 2 Baseline ≤0.5, rITT Population – Part 2

	Treatment Group			Pairwise Comparisons[a]		
Time Point	**E25+MTX n/N (%) 95% CI**	**MTX n/N (%) 95% CI**	**PBO n/N (%) 95% CI**	**E25 vs MTX P-Value OR (95% CI)**	**E25 vs PBO P-Value OR (95% CI)**	**MTX vs PBO P-Value OR (95% CI)**
Week 91	46/51 (90.2)	43/45 (95.6)	27/30 (90.0)	0.3254	0.9772	0.3569
	78.6, 96.7	84.9, 99.5	2.1, 26.5	0.43 (0.1, 2.3)	1.02 (0.2, 4.6)	2.39 (0.4, 15.2)
Final on therapy[b]	51/58 (87.9)	54/56 (96.4)	44/49 (89.8)	0.1124	0.7609	0.1929
	76.7, 95.0	87.7, 99.6	77.8, 96.6	0.27 (0.1, 1.4)	0.83 (0.2, 2.8)	3.07 (0.6, 16.6)

CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); N = number of subjects in the treatment group; n = number of subjects in each criteria; OR = odds ratio; PBO=placebo etanercept + placebo methotrexate (group); rITT = radiographic intent-to-treat.

a. Odds ratios and p-values for pairwise treatment comparisons at the Week 91 visit were based on a logistic regression statistical model with one factor (treatment).

b. Final on-therapy comparisons were based on a logistic regression model with treatment only as a factor in the model.

Table 46. Modified Total Sharp Score: Between-Group Comparison of Change From Part 2 Baseline, rITT Population – Part 2

	Treatment Group			Pairwise Comparison[a]		
Time Point	E25+MTX n Raw Mean (SD) Adj Change (SE)	MTX n Raw Mean (SD) Adj Change (SE)	PBO n Raw Mean (SD) Adj Change (SE)	E25 vs MTX P-Value Diff (95% CI)	E25 vs PBO P-Value Diff (95% CI)	MTX vs PBO P-Value Diff (95% CI)
Week 52[b]	58 8.4 (13.5)	56 8.4 (15.1)	49 8.6 (12.8)	0.7364	0.8218	0.5853
Week 91	51 9.3 (14.0) 0.0 (0.21)	45 8.7 (16.1) 0.0 (0.22)	30 9.1 (16.2) 0.7 (0.27)	0.9547 -0.02 (-0.6, 0.6)	0.2254 -0.66 (-1.3, 0.0)	0.2171 -0.64 (-1.3, 0.1)
Final on therapy	58 8.5 (13.3) 0.1 (0.33)	56 8.0 (15.6) -0.4 (0.34)	49 9.0 (13.9) 0.4 (0.36)	0.7713 0.51 (-0.4, 1.4)	0.5222 -0.32 (-1.3, 0.7)	0.3618 -0.82 (-1.8, 0.2)

Adj = adjusted; ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; Diff = mean difference; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); n = number of subjects in each criteria; PBO = placebo etanercept + placebo methotrexate (group); rITT = radiographic intent-to-treat; SD = standard deviation; SE = standard error

a. Adjusted means, mean differences (Diff) at Week 91 and final on-therapy visits were based on an ANCOVA model with factors for Week 52 value as baseline, and treatment. P-values for between-treatment comparisons were based on ANCOVA on ranks of change in score with ranks of Week 52 value as covariate.

b. Week 52 pairwise comparison p-values were from a single factor (treatment) ANOVA on ranked values.

Safety Results:

Extent of Exposure:

Part 1:

Table 47 and Table 48 presents the mean (SD) weekly dose of ETN and MTX respectively.

Table 47. Mean Weekly Dose of Etanercept in Part 1

Statistic	ETN 50 mg/MTX
Mean weekly dose of ETN (mg)	
N	306
Mean	49.47
SD	1.41
SE	0.08
Median	50.00
Min, Max	37.50, 50.00

Weekly dose (mg) for each subject = (total number of injections/number of weeks on treatment in Part 1) x 50.
Number of weeks on treatment in Part 1 = (Part 1 therapy stop date - Part 1 therapy start date + 1)/7.
Note: For each ETN record: Number of injections = (stop date - start date + 1)/7. Total number of injections = sum (number of injections) for each subject.
ETN = etanercept; Max = maximum; Min = minimum; MTX = methotrexate; N = total number of subjects entered in the study; SD = standard deviation; SE = standard error.

Table 48. Mean Weekly Dose of Methotrexate in Part 1

Statistic	ETN 50 mg/MTX
Mean weekly dose of MTX (mg)	
N	306
Mean	16.41
SD	4.79
SE	0.27
Median	17.54
Min, Max	4.38, 24.43

ETN = etanercept; Max = maximum; Min = minimum; MTX = methotrexate; N = total number of subjects entered in the study; SD = standard deviation; SE = standard error.

Part 2:

Table 49 and Table 50 present extent of exposure for Part 2 of the study. Table 51 shows cumulative exposure in Part 2 to any investigational product was 41.744, 39.604, and 34.222 subject-years for subjects in the E25+MTX, MTX, and PBO treatment groups, respectively.

Part 3:

Table 52 presents extent of exposure for Part 3 of the study.

Table 49. Mean Weekly Dose of Injectable Investigational Product (Etanercept or Placebo Equivalent) Administered in Part 2

Statistic	E25+MTX (N=63)	MTX (N=65)	PBO (N=65)
Mean weekly dose (mg)			
N	63	65	65
Mean	24.78	24.93	24.94
SD	0.67	0.26	0.27
SE	0.08	0.03	0.03
Median	25.00	25.00	25.00
Min, max	21.62, 25.00	23.68, 25.00	23.08, 25.00

For each etanercept record: Number of injections = (stop date - start date + 1)/7. Total number of injections = sum (number of injections) for each subject.
Weekly dose (mg) for each subject = (total number of injections/number of weeks on treatment in Part 2) x 25.
Number of weeks on treatment in Part 2 = (Part 2 therapy stop date - Part 2 therapy start date + 1)/7.
E25+MTX = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); PBO = placebo etanercept + placebo methotrexate (group); max = maximum; min = minimum; SD = standard deviation; SE = standard error.

Table 50. Mean Weekly Dose of Oral Investigational Product (Methotrexate or Placebo Equivalent) Administered in Part 2

Statistic	E25+MTX (N=63)	MTX (N=65)	PBO (N=65)
Mean weekly dose (mg)			
N	63	65	65
Mean	17.72	17.20	17.15
SD	4.99	5.54	5.37
SE	0.63	0.69	0.67
Median	20.00	16.54	20.00
Min, max	9.59, 25.00	10.00, 25.00	10.00, 30.00

For each methotrexate record: Number of weeks on treatment = (stop date - start date + 1)/7.
Mean weekly dose (mg) per subject: Total dose/number of weeks of methotrexate received. Total dose = Number of capsules x 5 mg.
Number of weeks on treatment in Phase 2 = (Phase 2 therapy stop date - Phase 2 therapy start date + 1)/7.E25+MTX = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); PBO=placebo etanercept + placebo methotrexate (group); max = maximum; min = minimum; SD = standard deviation; SE = standard error.

Table 51. Summary of Exposure to Injectable or Oral Investigational Product, by 28-Day Interval

Treatment Group	Interval	Total Number of Subjects	Percent of Subjects (%)	Subject-Years
E25+MTX	Days 0-28	63	100	4.528
	Days 29-56	59	93.7	4.523
	Days 57-84	59	93.7	4.471
	Days 85-112	58	92.1	4.400
	Days 113-140	57	90.5	4.370
	Days 141-168	57	90.5	4.246
	Days 169-196	54	85.7	4.140
	Days 197-224	54	85.7	4.129
	Days 225-252	53	84.1	4.063
	Days 253-280	53	84.1	2.847
	Days 281-308	4	6.3	0.027
	Total			41.744
MTX	Days 0-28	65	100	4.753
	Days 29-56	60	92.3	4.586
	Days 57-84	59	90.8	4.359
	Days 85-112	55	84.6	4.140
	Days 113-140	53	81.5	4.063
	Days 141-168	53	81.5	4.003
	Days 169-196	51	78.5	3.797
	Days 197-224	49	75.4	3.715
	Days 225-252	47	72.3	3.603
	Days 253-280	47	72.3	2.552
	Days 281-308	3	4.6	0.033
	Total			39.604
PBO	Days 0-28	65	100	4.810
	Days 29-56	62	95.4	4.611
	Days 57-84	60	92.3	4.342
	Days 85-112	52	80	3.723
	Days 113-140	45	69.2	3.433
	Days 141-168	43	66.2	3.220
	Days 169-196	39	60	2.817
	Days 197-224	36	55.4	2.760
	Days 225-252	36	55.4	2.705
	Days 253-280	35	53.8	1.796
	Days 281-308	1	1.5	0.005
	Total			34.222

E25+MTX = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept + methotrexate (group); PBO = placebo etanercept + placebo methotrexate (group).
The therapy start date,stop date and duration are for etanercept and methotrexate dosing.
Subject-years are based on the earliest dose and the last dose of either etanercept or methotrexate.

Table 52. Summary Tabulation of Mean Weekly Dose of Oral Test Article

Statistic	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)
Mean weekly dose (mg)			
N	51	46	32
Mean	13.15	11.61	11.34
SD	4.31	3.41	3.79
SE	0.60	0.50	0.67
Median	12.50	10.00	10.00
Min, max	7.50, 25.00	5.00, 19.00	7.50, 20.00

For each MTX record: Number of weeks on treatment in each period = (stop date - start date +1)/7. Mean weekly dose (mg) per subject: Total dose/number of weeks of MTX received.
Total Dose = Number of capsules x 5 mg.
Number of weeks in Part 3 = (Part 3 therapy stop date - Part 3 therapy start date + 1)/7.
CI = confidence interval; E25+MTX or E25 = etanercept 25 mg + methotrexate (group); mITT = modified intent-to-treat; MTX = placebo etanercept+methotrexate (group); NE = not estimable; PBO = placebo etanercept + placebo methotrexate (group).

Part 1:

AEs and SAEs reported in the study are presented in Table 53 and Table 54.
Treatment realted AEs are present in Table 55. There were no deaths in Part 1 of the study.
Twenty subjects (6.5%) were withdrawn from the study in Part 1 due to TEAEs (including Investigator-identified infections as indicated in Table 56).

Table 53. Number (%) of Subjects Reporting ≥ 5 % Treatment Emergent Non-Serious Adverse Events (Including Infections)

System Organ Class[a] Preferred Term	Treatment Etanercept 50 QW+Methotrexate n=306
Any Adverse Event	130 (42.5)
Gastrointestinal disorders	39 (12.7)
Nausea	39 (12.7)
General disorders and administration site conditions	36 (11.8)
Injection site erythema	17 (5.6)
Injection site reaction	19 (6.2)
Infections and infestations	52 (17.0)
Nasopharyngitis	39 (12.7)
Upper respiratory tract infection	17 (5.6)
Investigations	17 (5.6)
Alanine amino transferase increased	17 (5.6)
Nervous system disorders	20 (6.5)
Headache	20 (6.5)
Respiratory thoracic and mediastinal disorders	18 (5.9)
Cough	18 (5.9)

Classification of adverse events are based on the medical dictionary for regulatory activities. Since a subject may report two or more adverse events within the higher level category
QW = Once daily; 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 2 or more adverse events within the higher level category.

Table 54. Number (%) of Subjects Reporting Serious Adverse Events

System Organ Class[a] Preferred Term	ETN 50 mg/MTX (N=306)
Any serious adverse event	28 (9.2)
Cardiac disorders	3 (1.0)
Acute myocardial infarction	1 (0.3)
Cardiac failure	1 (0.3)
Coronary artery disease	2 (0.7)
Eye disorders	1 (0.3)
Cataract	1 (0.3)
Gastrointestinal disorders	5 (1.6)
Abdominal pain	1 (0.3)
Diarrhoea	1 (0.3)
Gastritis erosive	1 (0.3)
Inguinal hernia	1 (0.3)
Upper gastrointestinal haemorrhage	1 (0.3)
General disorders and administration site conditions	1 (0.3)
Asthenia	1 (0.3)
Infections and infestations	6 (2.0)
Abscess	1 (0.3)
Bronchitis	1 (0.3)
Empyema	1 (0.3)
Infected cyst	1 (0.3)
Lower respiratory tract infection viral	1 (0.3)
Pneumonia	1 (0.3)
Soft tissue infection	1 (0.3)
Injury, poisoning and procedural complications	2 (0.7)
Foot fracture	1 (0.3)
Upper limb fracture	1 (0.3)
Metabolism and nutrition disorders	1 (0.3)
Dehydration	1 (0.3)
Musculoskeletal and connective tissue disorders	7 (2.3)
Back pain	1 (0.3)
Intervertebral disc protrusion	1 (0.3)
Muscle spasms	1 (0.3)
Osteoarthritis	2 (0.7)
Systemic sclerosis	1 (0.3)
Tendon disorder	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.0)
Ovarian cancer	1 (0.3)
Pituitary tumour benign	1 (0.3)
Prostate cancer	1 (0.3)
Uterine cancer	1 (0.3)
Nervous system disorders	2 (0.7)
Headache	1 (0.3)
Loss of consciousness	1 (0.3)
Pregnancy, puerperium and perinatal conditions	1 (0.3)
Abortion spontaneous	1 (0.3)
Psychiatric disorders	1 (0.3)
Psychiatric decompensation	1 (0.3)
Reproductive system and breast disorders	1 (0.3)
Endometrial hyperplasia	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)
Pleural effusion	1 (0.3)

Table 54. Number (%) of Subjects Reporting Serious Adverse Events

AE = adverse event; ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities;
MTX = methotrexate; N = total number of subjects entered in the study.
Classifications of AEs are based on MedDRA.

a. Totals for the numbers 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 AEs within the higher level category.

Table 55. Treatment-Emergent Treatment-Related Adverse Events

System Organ Class[a] Preferred Term[b]	ETN 50 mg/MTX (N=306)
Any adverse event	135 (44.1)
Blood and lymphatic system disorders	5 (1.6)
‘ Anaemia	1 (0.3)
Leukopenia	3 (1.0)
Lymphadenopathy	1 (0.3)
Ear and labyrinth disorders	2 (0.7)
Vertigo	2 (0.7)
Eye disorders	3 (1.0)
Conjunctivitis	2 (0.7)
Vision blurred	1 (0.3)
Gastrointestinal disorders	39 (12.7)
Abdominal discomfort	1 (0.3)
Abdominal pain	1 (0.3)
Abdominal pain upper	3 (1.0)
Apical granuloma	1 (0.3)
Diarrhoea	9 (2.9)
Dry mouth	1 (0.3)
Dyspepsia	4 (1.3)
Gastritis erosive	1 (0.3)
Gastrooesophageal reflux disease	1 (0.3)
Gingivitis	1 (0.3)
Mouth ulceration	1 (0.3)
Nausea	35 (11.4)
Periodontitis	1 (0.3)
Vomiting	3 (1.0)
General disorders and administration site conditions	54 (17.6)
Asthenia	2 (0.7)
Chills	1 (0.3)
Drug intolerance	2 (0.7)
Fatigue	8 (2.6)
Impaired healing	1 (0.3)
Influenza like illness	1 (0.3)
Injection site erythema	17 (5.6)
Injection site irritation	1 (0.3)
Injection site pain	2 (0.7)
Injection site pruritus	3 (1.0)
Injection site rash	2 (0.7)
Injection site reaction	19 (6.2)
Malaise	1 (0.3)
Non-cardiac chest pain	1 (0.3)
Oedema peripheral	2 (0.7)
Pain	1 (0.3)
Pyrexia	2 (0.7)
Infections and infestations	66 (21.6)
Abscess	1 (0.3)
Acute sinusitis	1 (0.3)
Bronchitis	6 (2.0)
Candidiasis	3 (1.0)
Cystitis	1 (0.3)
Ear infection	2 (0.7)
Empyema	1 (0.3)

Table 55. Treatment-Emergent Treatment-Related Adverse Events

System Organ Class[a] Preferred Term[b]	ETN 50 mg/MTX (N=306)
Furuncle	1 (0.3)
Genitourinary tract infection	1 (0.3)
Herpes zoster	1 (0.3)
Infected cyst	1 (0.3)
Influenza	4 (1.3)
Laryngitis	2 (0.7)
Lower respiratory tract infection	7 (2.3)
Lower respiratory tract infection viral	1 (0.3)
Nasopharyngitis	16 (5.2)
Oral herpes	3 (1.0)
Oropharyngitis fungal	1 (0.3)
Pharyngitis	7 (2.3)
Pneumonia	2 (0.7)
Pyelonephritis	1 (0.3)
Respiratory tract infection	1 (0.3)
Rhinitis	5 (1.6)
Sinusitis	5 (1.6)
Soft tissue infection	1 (0.3)
Tooth abscess	3 (1.0)
Tracheitis	2 (0.7)
Upper respiratory tract infection	10 (3.3)
Urinary tract infection	8 (2.6)
Vulvovaginal mycotic infection	1 (0.3)
Injury, poisoning and procedural complications	1 (0.3)
Procedural headache	1 (0.3)
Investigations	23 (7.5)
Alanine Aminotransferase Increased	15 (4.9)
Aspartate aminotransferase increased	8 (2.6)
Blood bilirubin increased	1 (0.3)
Gamma-glutamyltransferase increased	3 (1.0)
Liver function test abnormal	3 (1.0)
Transaminases increased	1 (0.3)
Waist circumference increased	1 (0.3)
Weight increased	2 (0.7)
White blood cell count decreased	1 (0.3)
Metabolism and nutrition disorders	3 (1.0)
Decreased appetite	1 (0.3)
Hypercholesterolaemia	1 (0.3)
Hyperlipidaemia	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.3)
Musculoskeletal pain	1 (0.3)
Nervous system disorders	7 (2.3)
Headache	8 (2.6)
Pregnancy, puerperium and perinatal conditions	1 (0.3)
Abortion spontaneous	1 (0.3)
Pregnancy	1 (0.3)
Reproductive system and breast disorders	3 (1.0)
Menstrual disorder	1 (0.3)
Metrorrhagia	1 (0.3)
Vaginal ulceration	1 (0.3)
Respiratory thoracic and mediastinal disorders	12 (3.9)
Cough	4 (1.3)

Table 55. Treatment-Emergent Treatment-Related Adverse Events

System Organ Class[a] Preferred Term[b]	ETN 50 mg/MTX (N=306)
Dyspnoea	2 (0.7)
Epistaxis	1 (0.3)
Nasal congestion	1 (0.3)
Oropharyngeal blistering	1 (0.3)
Oropharyngeal pain	4 (1.3)
Pleurisy	1 (0.3)
Productive cough	1 (0.3)
Skin and subcutaneous tissue disorders	28 (9.2)
Acne	1 (0.3)
Alopecia	11 (3.6)
Blister	1 (0.3)
Dermatitis allergic	3 (1.0)
Dry skin	2 (0.7)
Erythema	2 (0.7)
Generalised erythema	1 (0.3)
Lichenoid keratosis	1 (0.3)
Night sweats	1 (0.3)
Onychoclasis	1 (0.3)
Pigmentation disorder	1 (0.3)
Rash	5 (1.6)
Rosacea	1 (0.3)
Skin chapped	1 (0.3)
Skin lesion	1 (0.3)
Skin reaction	1 (0.3)
Toxic skin eruption	1 (0.3)
Umbilical erythema	1 (0.3)
Vascular disorders	2 (0.7)
Flushing	1 (0.3)
Hypertension	1 (0.3)

AEs and SAEs are not separated out in the table.
Classifications of Adverse Events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
AEs = adverse events; ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = total number of subjects entered in the study; SAEs = serious adverse events.

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 two or more adverse events within the higher level category.
b. For each Subject, adverse events were reported for the highest drug relationship within the highest severity (first priority) observed.

Table 56. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (Including Infections) Causing Withdrawal

System Organ Class[a] Preferred Term	ETN 50 mg/MTX (N=306)
Any TEAE causing withdrawal	20 (6.5)
Blood and lymphatic system disorders	1 (0.3)
Leukopenia	1 (0.3)
Gastrointestinal disorders	2 (0.7)
Abdominal pain upper	1 (0.3)
Diarrhoea	1 (0.3)
Dyspepsia	1 (0.3)
General disorders and administration site conditions	3 (1.0)
Injection site erythema	1 (0.3)
Injection site rash	1 (0.3)
Injection site reaction	1 (0.3)
Infections and infestations	3 (1.0)
Abscess	1 (0.3)
Infected cyst	1 (0.3)
Pneumonia	1 (0.3)
Investigations	1 (0.3)
Alanine aminotransferase increased	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.7)
Osteoarthritis	1 (0.3)
Systemic sclerosis	1 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.0)
Ovarian cancer	1 (0.3)
Pituitary tumour benign	1 (0.3)
Prostate cancer	1 (0.3)
Uterine cancer	1 (0.3)
Pregnancy, puerperium and perinatal conditions	3 (1.0)
Abortion spontaneous	1 (0.3)
Pregnancy	3 (1.0)
Skin and subcutaneous tissue disorders	2 (0.7)
Generalised erythema	1 (0.3)
Toxic skin eruption	1 (0.3)

Classifications of AEs are based on MedDRA.
AE = adverse event; ETN = etanercept; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; N = total number of subject entered in the study; TEAE = treatment-emergent adverse event.
a. Totals for the numbers 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 AEs within the higher level category.

Twenty-five (25) subjects (8.2%) reported AEs during Phase 1 that required hospitalization, including 5 subjects (1.6%) with investigator-identified infections. Seven (7) subjects (2.3%) had latent TB; none of these events were treatment emergent. One (1) subject (0.3%) had herpes zoster; the event was treatment emergent, moderate in intensity, and in the opinion of the investigator was related to treatment with investigational product. Two (2) subjects (0.7%) reported 3 malignancies in Phase 1. There were no cases of demyelinating diseases.

Deaths: There were no deaths reported during Part 1 of the study.

Part 2:

Table 57 presents the non-serious AEs reported in ≥5% subjects and treatment related events in Table 58. Pairwise comparisons of the number (%) of subjects reporting tier-1 AEs are presented in Table 59, Table 60, and Table 61 for the E25+MTX vs PBO, E25+MTX vs MTX, and MTX vs PBO treatment groups, respectively. The risk differences for 'alanine aminotransferase increased,' the only tier-1 AE reported during Part 2, were not statistically significant for any of the 3 pairwise comparisons. Pairwise comparisons of the number (%) of subjects reporting tier-2 AEs are presented in Table 62, Table 63, and Table 64 for the E25+MTX vs PBO, E25+MTX vs MTX, and MTX vs PBO treatment groups, respectively. The 95% CIs of the risk differences for all of the pairwise comparisons for nasopharyngitis, upper respiratory tract infection, and RA included zero; therefore the risk differences were not statistically significant. Table 65 shows serious adverse event occurred in Part 2 of the study.

Table 57. Number (%) of Subjects Reporting ≥5% Treatment Emergent Non-Serious Adverse Events (Including Infections)

System Organ Class[a] Preferred Term	E25+MTX (N=63)	MTX (N=65)	PBO (N=65)
Any adverse event	10 (15.9)	8 (12.3)	11 (16.9)
Infections and infestations	8 (12.7)	6 (9.2)	6 (9.2)
Nasopharyngitis	5 (7.9)	3 (4.6)	3 (4.6)
Upper respiratory tract infection	4 (6.3)	3 (4.6)	3 (4.6)
Musculoskeletal and connective tissue disorders	2 (3.2)	2 (3.1)	6 (9.2)
Rheumatoid arthritis	2 (3.2)	2 (3.1)	6 (9.2)

E25+MTX or E25=etanercept 25 mg+methotrexate (group); MTX=placebo etanercept+methotrexate (group); PBO=placebo etanercept+placebo methotrexate (group).

a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a Subject may report two or more Adverse Events within the higher level category.

Table 58. Treatment Emergent Treatment Related Adverse Events

System Organ Class[a] Preferred Term[b]	E25+MTX (n=63)	MTX (n=65)	PBO (n=65)	Total (n=193)
Any adverse event	19 (30.2)	11 (16.9)	11 (16.9)	41 (21.2)
Cardiac disorders	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Pericarditis	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Gastrointestinal disorders	3 (4.8)	3 (4.6)	0 (0.0)	6 (3.1)
Abdominal distension	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Nausea	2 (3.2)	2 (3.1)	0 (0.0)	4 (2.1)
Oesophagitis	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Infections and infestations	11 (17.5)	6 (9.2)	10 (15.4)	27 (14.0)
Acute tonsillitis	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Bacterial pyelonephritis	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Bronchitis	2 (3.2)	0 (0.0)	1 (1.5)	3 (1.6)
Candidiasis	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Cystitis	0 (0.0)	1 (1.5)	2 (3.1)	3 (1.6)
Ear infection	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Herpes zoster	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Influenza	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.0)
Laryngitis	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Lower respiratory tract infection	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.0)
Nasopharyngitis	4 (6.3)	1 (1.5)	0 (0.0)	5 (2.6)
Otitis externa	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Otitis media	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Pharyngitis	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.0)
Rhinitis	1 (1.6)	0 (0.0)	1 (1.5)	2 (1.0)
Subcutaneous abscess	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Tooth abscess	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.0)
Upper respiratory tract infection	2 (3.2)	2 (3.1)	2 (3.1)	6 (3.1)
Urinary tract infection	1 (1.6)	1 (1.5)	3 (4.6)	5 (2.6)
Investigations	4 (6.3)	3 (4.6)	0 (0.0)	7 (3.6)
Alanine aminotransferase increased	3 (4.8)	1 (1.5)	0 (0.0)	4 (2.1)
Aspartate aminotransferase increased	2 (3.2)	1 (1.5)	0 (0.0)	3 (1.6)
Gamma-glutamyltransferase increased	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Hepatic enzyme increased	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.0)
White blood cell count decreased	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.5)	2 (3.1)	3 (1.6)
Bone swelling	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Rheumatoid arthritis	0 (0.0)	1 (1.5)	1 (1.5)	2 (1.0)
Renal and urinary disorders	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Renal Pain	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Cough	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)

AEs and SAEs are not separated out.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
E25+MTX or E25 = etanercept 25 mg + methotrexate (group); MTX = placebo etanercept+methotrexate (group); PBO = placebo etanercept+placebo methotrexate (group).

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 two or more adverse events within the higher level category.
b. For each subject, adverse events are reported for the highest drug relationship within the highest severity (first priority) observed.

Table 59. Number (%) of Subjects Reporting Tier-1 Adverse Events, Pairwise Comparison of the E25+MTX and PBO Treatment Groups

	Treatment			95% Confidence Interval		
System Organ Class Preferred Term	E25+MTX (N=63) n (%)	PBO (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit	p-Value
Investigations	-	-	-	-	-	-
Alanine aminotransferase increased	3 (4.8)	0 (0.0)	0.048	-0.011	0.134	0.0878

Tier-1 AEs are pre-specified events of clinical importance.
Per adjudication guidelines, the AE of herpes zoster for one subject (PBO treatment group) was not included in this tier-1 report, as only 1 dermatome was affected. The event is included in the tier-3 report
p-values and CIs were not adjusted for multiplicity and was used for screening purposes only.
95% CIs were provided to help guage the precision of the estimate for treatment difference (risk difference).
The risk difference was computed as E25+MTX minus PBO.
AE = adverse event; CI = confidence interval; E25+MTX = etanercept 25 mg+methotrexate (group);
N = number of subjects; n = number of subjects with specified events; PBO = placebo etanercept + placebo methotrexate (group).

Table 60. Number (%) of Subjects Reporting Tier-1 Adverse Events, Pairwise Comparison of the E25+MTX and MTX Treatment Groups

	Treatment			95% Confidence Interval		
System Organ Class Preferred Term	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit	p-Value
Investigations	-	-	-	-	-	-
Alanine aminotransferase increased	3 (4.8)	2 (3.1)	0.017	-0.066	0.106	0.7290

Tier-1 AEs are pre-specified events of clinical importance. p-values and CIs were not adjusted for multiplicity and should be used for screening purposes only.
95% CIs were provided to help guage the precision of the estimate for treatment difference (risk difference).
The risk difference was computed as E25+MTX minus MTX.
AE = adverse event; CI = confidence interval; E25+MTX = etanercept 25 mg+methotrexate (group);
MTX = placebo etanercept+methotrexate (group).

Table 61. Number (%) of Subjects Reporting Tier-1 Adverse Events, Pairwise Comparison of the MTX and PBO Treatment Groups

	Treatment			95% Confidence Interval		
System Organ Class Preferred Term	MTX (N=65) n (%)	PBO (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit	p-Value
Investigations	-	-	-	-	-	-
Alanine aminotransferase increased	2 (3.1)	0 (0.0)	0.031	-0.027	0.107	0.2096

Tier-1 AEs are pre-specified events of clinical importance.
Per adjudication guidelines, the AE of herpes zoster for 1 subject (PBO treatment group) was not included in this tier-1 report, as only 1 dermatome was affected. The event was included in the tier-3 report
p-values and CIs were not adjusted for multiplicity and should be used for screening purposes only.
95% CIs were provided to help guage the precision of the estimate for treatment difference (risk difference).
The risk difference was computed as MTX minus PBO.
AE = adverse event; CI = confidence interval; MTX = placebo etanercept+methotrexate (group);
PBO = placebo etanercept + placebo methotrexate (group).

Table 62. Adverse Events Reported by ≥5% of Subjects (Tier-2 Adverse Events), Pairwise Comparison of the E25+MTX and PBO Treatment Groups

	Treatment			95% Confidence Interval	
System Organ Class Preferred Term	E25+MTX (N=63) n (%)	PBO (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit
Infections and infestations	-	-	-	-	-
Nasopharyngitis	5 (7.9)	3 (4.6)	0.033	-0.060	0.135
Upper respiratory tract infection	4 (6.3)	3 (4.6)	0.017	-0.074	0.118
Musculoskeletal and connective tissue disorders	-	-	-	-	-
Rheumatoid arthritis	2 (3.2)	7 (10.8)	-0.076	-0.181	0.017

CIs were not adjusted for multiplicity and should be used for screening purposes only.
95% CIs are provided to help guage the precision of the estimate for treatment difference (risk difference).
The risk difference is computed as E25+MTX minus PBO.
CI = confidence interval; E25+MTX = etanercept 25 mg+methotrexate (group); PBO placebo etanercept + placebo methotrexate (group).

Table 63. Adverse Events Reported by ≥5% of Subjects (Tier-2 Adverse Events), Pairwise Comparison of the E25+MTX and MTX Treatment Groups

	Treatment			95% Confidence Interval	
System Organ Class Preferred Term	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit
Infections and infestations	-	-	-	-	-
Nasopharyngitis	5 (7.9)	3 (4.6)	0.033	-0.060	0.135
Upper respiratory tract infection	4 (6.3)	3 (4.6)	0.017	-0.074	0.118
Musculoskeletal and connective tissue disorders	-	-	-	-	-
Rheumatoid arthritis	2 (3.2)	2 (3.1)	-	-	-

CIs were not adjusted for multiplicity and should be used for screening purposes only.
95% CIs are provided to help guage the precision of the estimate for treatment difference (risk difference). The risk difference is computed as E25+MTX minus MTX.
CI = confidence interval; E25+MTX = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept + methotrexate (group); N = number of subjects; n = number of subjects in the specified criteria.

Table 64. Adverse Events Reported by ≥5% of Subjects (Tier-2 Adverse Events), Pairwise Comparison of the MTX and PBO Treatment Groups

	Treatment			95% Confidence Interval	
System Organ Class Preferred Term	MTX (N=65) n (%)	PBO (N=65) n (%)	Risk Difference	Lower Limit	Upper Limit
Infections and infestations	-	-	-	-	-
Nasopharyngitis	3 (4.6)	3 (4.6)	-	-	-
Upper respiratory tract infection	3 (4.6)	3 (4.6)	-	-	-
Musculoskeletal and connective tissue disorders	-	-	-	-	-
Rheumatoid arthritis	2 (3.1)	7 (10.8)	-0.077	-0.182	0.013

CIs were not adjusted for multiplicity and should be used for screening purposes only.
95% CIs are provided to help guage the precision of the estimate for treatment difference (risk difference). The risk difference is computed as MTX minus PBO.
CI = confidence interval; MTX = placebo etanercept+methotrexate (group); N = number of subjects; n = number of subjects in the specified criteria; PBO = placebo etanercept + placebo methotrexate (group).

Table 65. Number (%) of Subjects Reporting Serious Adverse Events (Including Investigator-Identified Infections)

System Organ Class[a] Preferred Term	Overall p-Value	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	PBO (N=65) n (%)	Total (N=193) n (%)
Any adverse event	0.8424	3 (4.8)	2 (3.1)	2 (3.1)	7 (3.6)
Cardiac disorders	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Pericarditis	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Ear and labyrinth disorders	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Ear canal stenosis postoperative	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Gastrointestinal disorders	0.3736	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Anal fissure	0.3736	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Infections and infestations	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Bacterial pyelonephritis	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Injury, poisoning and procedural complications	0.3736	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Femoral neck fracture	0.3736	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0.3736	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Rheumatoid arthritis	0.3736	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Nervous system disorders	0.3736	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Headache	0.3736	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Reproductive system and breast disorders	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Cystocele	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)

Classifications of AEs are based on MedDRA.
AE = adverse event; E25+MTX = etanercept 25 mg+methotrexate (group); MedDRA = Medical Dictionary for Regulatory Activities; MTX = placebo etanercept+methotrexate (group); N = number of subjects; n = number of subjects in the specified criteria; PBO = placebo etanercept + placebo methotrexate (group).
a. Totals for the numbers 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 AEs within the higher level category.

One serious adverse event, pericarditis, was considered treatment related in Part 2 of the study.

Table 66 shows permanent discontinuations due to adverse events in Part 2 of the study. There were no deaths in Part 2 of the study.

Table 66. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (Including Investigator-Identified Infections) Causing Withdrawal

System Organ Class[a] Preferred Term	Overall p-Value	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	PBO (N=65) n (%)	Total (N=193) n (%)
Any adverse event	0.1976	4 (6.3)	1 (1.5)	1 (1.5)	6 (3.1)
Cardiac disorders	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Pericarditis	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Infections and infestations	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Bacterial pyelonephritis	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Investigations	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Alanine aminotransferase increased	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Aspartate aminotransferase increased	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Gamma-glutamyltransferase increased	0.3564	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Musculoskeletal and connective tissue disorders	0.9997	1 (1.6)	1 (1.5)	1 (1.5)	3 (1.6)
Rheumatoid arthritis	0.9997	1 (1.6)	1 (1.5)	1 (1.5)	3 (1.6)

Classifications of AEs are based on MedDRA.
AE = adverse event; E25+MTX = etanercept 25 mg+methotrexate (group); MedDRA = Medical Dictionary for Regulatory Activities; MTX = placebo etanercept+methotrexate (group); N = number of subjects; n = number of subjects in the specified criteria; PBO = placebo etanercept+placebo methotrexate (group).
a. Totals for the numbers 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 AEs within the higher level category.

Part 3:

Table 67 presents non-serious adverse events in part 3 of the study along with treatment related events in Table 68.

Table 67. Number (%) of Subjects Reporting ≥5% Treatment Emergent Non-Serious Adverse Events (Including Infections)

System Organ Class[a] Preferred Term	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)
Any adverse event	15 (28.3)	6 (13.0)	3 (9.4)
Infections and infestations	3 (5.7)	2 (4.3)	1 (3.1)
Investigations	2 (3.8)	3 (6.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	8 (15.1)	1 (2.2)	1 (3.1)
Rheumatoid arthritis	6 (11.3)	1 (2.2)	1 (3.1)

E25+MTX or E25 = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept+methotrexate (group); PBO = placebo etanercept+placebo methotrexate (group).
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 two or more Adverse Events within the higher level category.

Table 68. Treatment-Emergent Treatment-Related Adverse Events

System Organ Class Preferred Term	E25+MTX	MTX	PBO	Total
Preferred Term	**(n=53)**	**(n=46)**	**(n=32)**	**(n=131)**
Any adverse event	5 (9.4)	4 (8.7)	1 (3.1)	10 (7.6)
Eye disorders	1(1.9)	0 (2.2)	0 (0.0)	1 (0.8)
Chalazion	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Infections and infestations	2 (3.8)	2 (4.3)	1 (3.1)	5 (3.8)
Cellulitis	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Keratitis herpetic	0(0.0)	1(2.2)	0(0.0)	1(0.8)
Oral infection	0(0.0)	0(0.0)	1(3.1)	1(0.8)
Rhinitis	1(1.9)	0(0.0)	0 (0.0)	1 (0.8)
Urinary tract infection	0(0.0)	1(2.2)	0(0.0)	1(0.8)
Investigations	1(1.9)	1(2.2)	0 (0.0)	2 (1.5)
Alanine aminotransferase increased	0(0.0)	1(2.2)	0 (0.0)	1 (0.8)
Aspartate aminotransferase increased	0(0.0)	1(2.2)	0 (0.0)	1 (0.8)
Hepatic Enzyme Increased	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Musculoskeletal and connective tissue disorders	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Bursitis	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Skin Papilloma	1(1.9)	0(0.0)	0(0.0)	1(0.8)
Respiratory, thoracic and mediastinal disorders	0(0.0)	1(2.2)	0(0.0)	1(0.8)
Cough	0(0.0)	1(2.2)	0(0.0)	1(0.8)

E25+MTX or E25 = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept+methotrexate (group); n = number of subjects; PBO = placebo etanercept+placebo methotrexate (group).

Table 69 presents number of subjects reporting serious adverse events in Part 3 of the study. Oral infection was considered as treatment related. Table 70 shows treatment emergent adverse events causing withdrawal. There were no deaths in Part 3 of the study.

Table 69. Number (%) of Subjects Reporting Serious Adverse Events (Including Investigator-Identified Infections)

System Organ Class[a] Preferred Term	Overall p-Value	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)	Total (N=131)
Any adverse event	0.0443	0 (0.0)	0 (0.0)	2 (6.3)	2 (1.5)
Infections and infestations	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)
Oral Infection	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)
Vascular disorders	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)
Vasculitis	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)

E25+MTX or E25 = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept+methotrexate (group); N = number of subjects; PBO = placebo etanercept+placebo methotrexate (group).
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 Adverse Events within the higher level category.

Table 70. Number (%) of Subjects Reporting Treatment Emergent Adverse Events (Including Investigator-Identified Infections) Causing Withdrawal

System Organ Class[a] Preferred Term	Overall p-Value	E25+MTX (N=53)	MTX (N=46)	PBO (N=32)	Total (N=131)
Any adverse event	0.1461	4 (7.5)	0 (0.0)	1 (3.1)	5 (3.8)
Musculoskeletal and connective tissue disorders	0.0491	4 (7.5)	0 (0.0)	0 (0.0)	4 (3.1)
Rheumatoid arthritis	0.0491	4 (7.5)	0 (0.0)	0 (0.0)	4 (3.1)
Vascular disorders	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)
Vasculitis	0.2129	0 (0.0)	0 (0.0)	1 (3.1)	1 (0.8)

Classifications of adverse events were based on the Medical Dictionary for Regulatory Activities (MedDRA).
E25+MTX or E25 = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept+methotrexate (group); N = number of subjects; PBO = placebo etanercept+placebo methotrexate (group).
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 adverse events within the higher level category.

Part 1:

Regarding laboratory values Table 71 shows statistically significant increases in mean values at Week 52 from the mean baseline values in some liver function tests that were also considered to be clinically significant: ALT (+7.9 U/L), AST (+5.0 U/L), total bilirubin (+1.8 µmol/L), and direct bilirubin (+0.3 µmol/L). These changes are most likely attributable to MTX exposure in this MTX-naïve study population.

Table 71. Clinically Significant Changes From Baseline in Laboratory Values

		Week 52		Baseline		Change		
Analyte (Units)	N	Mean	SD	Mean	SD	Mean	SE	p-value[a]
ALT (U/L)	227	29.9	22.21	22.0	10.56	+7.9	1.36	<0.001
AST (U/L)	225	25.9	11.32	20.9	6.33	+5.0	0.73	<0.001
Bilirubin, total (µmol/L)	211	9.1	4.55	7.3	3.64	+1.8	0.25	<0.001
Bilirubin, direct (µmol/L)	111	2.6	0.91	2.3	0.76	+0.3	0.08	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of subjects with matching baseline; SD = standard deviation; SE = standard error.
a. Paired t-test for significant change from baseline.

Table 72 and Table 73 present Grade 3 or 4 laboratory test results and increases in AST, ALT, or alkaline phosphatase greater than two times the upper limit of normal.

Table 72. Number (%) of Subjects With Grade 3 or 4 Laboratory Test Results

Laboratory Test Category Analyte Grade	ETN 50 mg/MTX (N=306) n (%)
Any Grade 3 or 4 laboratory test result	13 (4.25)
Chemistry	12 (3.92)
ALT	6 (1.96)
Grade 3	6 (1.96)
AST	1 (0.33)
Grade 3	1 (0.33)
Bilirubin	3 (0.98)
Grade 3	3 (0.98)
Creatinine	1 (0.33)
Grade 3	1 (0.33)
Sodium	2 (0.65)
Grade 3	2 (0.65)
Hematology	1 (0.33)
Neutrophils	1 (0.33)
Grade 3	1 (0.33)

For each test only the maximum grade per subject was counted.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ETN = etanercept; MTX = methotrexate; N = total number of subject entered in the study; n = number of subjects in each criteria.

Table 73. Number (%) of Subjects With Increases in AST, ALT, or Alkaline Phosphatase Greater Than Two Times the Upper Limit of Normal

Analyte Elevation	ETN 50 mg/MTX n/N (%)
Any AST, ALT, or alkaline phosphatase increase >2 x ULN	35/306 (11.44)
AST	34/304 (11.18)
>3 x ULN	6/304 (1.97)
>2 x and ≤3 x ULN	28/304 (9.21)
ALT	17/304 (5.59)
>3 x ULN	3/304 (0.99)
>2 x and ≤3 x ULN	14/304 (4.61)
Alkaline phosphatase	1/305 (0.33)
>2 x and ≤3 x ULN	1/305 (0.33)

For an individual subject only the worst lab abnormality, within each lab test, was tabulated.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ETN = etanercept; MTX = methotrexate; N = number of subjects in the treatment group (ETN 50 mg+MTX); n = number of subjects in each criteria ULN = upper limit of normal.

Regarding analyses of vital signs and physical characteristics, statistically significant changes in mean values at Week 52 from the mean baseline values in vital signs and physical findings that were not considered to be clinically significant were observed for: diastolic blood pressure, systolic blood pressure, heart rate, BMI (female), hip circumference (female), and weight.

Part 2:

Table 74 and Table 75 show clinically significant laboratory abnormalities of Part 2 of the study.

Table 74. Number (%) of Subjects With Grade 3 or 4 Laboratory Test Results

Category Test Grade	E25+MTX (N=63) n (%)	MTX (N=65) n (%)	PBO (N=65) n (%)	Total (N=193) n (%)
Total	2 (3.17)	0 (0.00)	0 (0.00)	2 (1.04)
Chemistry	2 (3.17)	0 (0.00)	0 (0.00)	2 (1.04)
ALT	1 (1.59)	0 (0.00)	0 (0.00)	1 (0.52)
Grade 3	1 (1.59)	0 (0.00)	0 (0.00)	1 (0.52)
Bilirubin	1 (1.59)	0 (0.00)	0 (0.00)	1 (0.52)
Grade 3	1 (1.59)	0 (0.00)	0 (0.00)	1 (0.52)

For each test only the maximum grade per subject was counted.
ALT = alanine aminotransferase; E25+MTX = etanercept 25 mg+methotrexate (group); MTX = placebo etanercept+MTX (group); N = number of subjects; n = number of subjects in the specified criteria; PBO = placebo etanercept+placebo MTX (group).

Table 75. Number (%) of Subjects With Increases in AST, ALT, or Alkaline Phosphatase Greater Than Two Times the Upper Limit of Normal

Analyte Elevation	E25+MTX n/N (%)	MTX n/N (%)	PBO n/N (%)	Total n/N (%)
Number of subjects with AST, ALT, or ALK PHOS >2 x ULN	5/63 (7.94)	6/65 (9.23)	0/62 (0.00)	11/193 (5.70)
AST	5/62 (8.06)	5/63 (7.94)	0/62 (0.00)	10/187 (5.35)
>2 x and ≤3 x ULN	5/62 (8.06)	5/63 (7.94)		10/187 (5.35)
ALT	2/62 (3.23)	1/63 (1.59)	0/62 (0.00)	3/187 (1.60)
>2 x and ≤3 x ULN	2/62 (3.23)	1/63 (1.59)		3/187 (1.60)
Alk Phos	0/62 (0.00)	0/63 (0.00)	0/62 (0.00)	0/187 (0.00)

For an individual subject only the worst laboratory abnormality, within each laboratory test, was tabulated.
Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; E25+MTX = etanercept 25 mg MTX (group); MTX = placebo etanercept+MTX (group); N = number of subjects; n = number of subjects in the specified criteria; PBO = placebo etanercept+placebo MTX (group); ULN = upper limit of normal.

For vital signs and physical characteristics, the difference among the treatment groups for mean change from Week 52 for heart rate was statistically significant but not clinically significant. None of the other mean changes from Week 52 were statistically significant.

Part 3:

No subject had a Grade 3 or 4 laboratory test result. Table 76 present clinically significant laboratory abnormalities in Part 3 of the study.

Table 76. Number (%) of Subjects With Increases in AST, ALT, or Alkaline Phosphatase Greater Than Two Times the Upper Limit of Normal

Category/Test+Units	Treatment			
	E25+MTX	MTX	PBO	Total
Number of subjects with SGOT/AST,SGPT/ALT or ALK. PHOS >2 x ULN	1/53 (1.89)	0/46 (0.00)	1/32 (3.13)	2/131 (1.53)
SGOT/AST U/L	1/50 (2.00)	0/43 (0.00)	1/31 (3.23)	2/124 (1.61)
>3 x ULN	1/50 (2.00)	0/43 (0.00)	0/31 (0.00)	1/124 (0.81)
>2 x and ≤3 x ULN	0/50 (0.00)	0/43 (0.00)	1/31 (3.23)	1/124 (0.81)
SGPT/ALT U/L	1/50 (2.00)	0/43 (0.00)	0/31 (0.00)	1/124 (0.81)
>3 x ULN	0/50 (0.00)	0/43 (0.00)	0/31 (0.00)	0/124 (0.00)
>2 x and ≤3 x ULN	1/50 (2.00)	0/43 (0.00)	0/31 (0.00)	1/124 (0.81)
Alkaline phosphatase U/L	0/51 (0.00)	0/43 (0.00)	0/31 (0.00)	0/125 (0.00)
>2 x and ≤3 x ULN	0/51 (0.00)	0/43 (0.00)	0/31 (0.00)	0/125 (0.00)

For an individual subject only the worst lab abnormality, within each lab test, was tabulated.
Alk Phos = alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ETN=etanercept; E25+MTX=etanercept 25 mg MTX (group); MTX=placebo etanercept+MTX (group); PBO=placebo etanercept+placebo MTX (group; SGOT=Serum glutamic oxaloacetic transaminase; SGPT=Serum glutamic pyruvic transaminase; U/L; upper limit; ULN=upper limit of normal.

For vital signs and physical characteristics, there were few instances of statistically significant mean changes from baseline at Weeks 104 or 117, concerning body weight and body mass index variables. These were considered not clinically relevant by the sponsor.

CONCLUSIONS:

Part 1:

In this open-label study of subjects with moderate to severe early RA, combination etanercept+MTX therapy resulted in significant improvement of clinical, functional, and health outcome measures, with minimal radiographic progression. There were no unexpected safety issues, as the safety results were similar to those of previous trials with combination etanercept and MTX treatment.

Part 2:

In this randomized, double-blind study of subjects with moderate to severe early RA who achieved remission with ETN + MTX treatment during a 52-week open-label study phase, there was 23% to 63% DAS28 remission maintenance overall in the subsequent 39 weeks during which the etanercept dose was either reduced or withdrawn, and no clinically or statistically significant radiographic progression despite reduction or elimination of DMARD therapy. Subjects who continued to receive ETN + MTX treatment over the next 39 weeks had statistically significantly better clinical and biological RA- and health-related outcomes than did subjects who received placebo. There were no unexpected safety issues.

Part 3:

By the end of Part 3, there were no statistical or clinically meaningful differences observed among the 3 treatment groups for the majority of clinical endpoints. During the course of

Part 2, subjects in the ETN25+MTX group had a modest loss of efficacy measures compared to the MTX and PBO treatment groups, who experienced sharper declines. Similar losses of efficacy were noted upon the withdrawal of ETN25+MTX during Part 3. There were no unexpected safety or tolerability findings in this early RA subject population during Part 3 and no change in the risk-benefit profile for ETN.