Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Etanercept in Subjects with Rheumatoid Arthritis Who Have Had an Inadequate Response to Adalimumab or Infliximab Plus Methotrexate.

Summary

EudraCT number	2012-003644-71
Trial protocol	ES NL BE
Global end of trial date	22 August 2014

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	B1801355

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street, New York,, United States, NY 10017
Public contact	ClinicalTrials.gov Call Center, Pfizer Inc., +1 800718 1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	ClinicalTrials.gov Call Center, Pfizer Inc., +1 800718 1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2014
Global end of trial reached?	Yes
Global end of trial date	22 August 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of etanercept to placebo in inadequate responders to infliximab or adalimumab plus methotrexate (MTX) in all subjects and in subjects who are anti-drug antibody positive (ADA+) to one of these monoclonal antibodies (mAbs).

Protection of trial subjects:

It was highly recommended that all participants take folic acid supplementation at a dose of 5 to 10 mg/week, either as a single dose on one day or as divided doses over several days to help minimize the side effects associated with Methotrexate (MTX, consistent with local label and guidelines).

Background therapy:

The dose of oral MTX was to be ≥10 mg once daily and ≤25 mg once daily and stable for a minimum of 6 weeks before the baseline visit.
From the baseline to the Week 12 visit, the dose of oral MTX was to remain stable (eg, no increase or decrease) unless there was an adverse event (AE) related to MTX.
At the Week 12 and Week 16 visits, the dose of oral MTX could be increased by ≤5 mg once daily to a maximum dose of 25 mg once daily per investigator discretion.
After Week 16 and through Week 24, the dose was to remain stable (eg, no increase or decrease) unless there was an AE related to MTX.
If the subject experienced an AE possibly associated with MTX, dose reduction of MTX was permitted after consultation with the sponsor’s clinical team:
The dose of MTX could be decreased or temporarily suspended for up to 2 weeks as needed and if possible, was to be re-titrated to the dose taken prior to the AE. If this was not possible, a minimum of 7.5 mg once daily was required to stay in the study; otherwise, the subject was withdrawn from the study.

Evidence for comparator: -	
Actual start date of recruitment	24 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Belgium: 3

Worldwide total number of subjects	16
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this 24 week, multicenter, randomized, double-blind, placebo-controlled (Period 1), 2 period study, a total of 20 participants were screened, out of which 16 participants were randomized. Due to delayed enrollment and an insufficient number of participants, recruitment was terminated. Four participants were considered to be screen failures.

Pre-assignment

Screening details:

Eleven participants were randomly assigned to etanercept [ETN] and 5 participants to placebo in the blinded treatment period. A total of 11 participants (9 ETN treated and 2 placebo treated) completed the blinded treatment period and entered the open label treatment with ETN. One of the 2 placebo treated participants entered the Escape Arm.

Pre-assignment period milestones

Number of subjects started	20[1]
Number of subjects completed	16

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failures: 4

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Twenty participants had been screened, of which 16 participants were enrolled. Four participants did not meet the eligibility criteria.

Period 1

Period 1 title	Period 1, Blinded Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Etanercept

Arm description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.

Arm type	Active comparator
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigational product will be administered by the subject or a qualified designee. At the baseline visit, the initial dose of etanercept/placebo investigational product must be
administered in the office by study personnel after all baseline evaluations have been completed, while the subject (or designee) observes.The etanercept or matching placebo was to be administered QW on the same day of the week throughout the study.

Arm title	Placebo

Arm description:

Participants received placebo injections with oral methotrexate tablets once-weekly.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

The etanercept or matching placebo was administered QW on the same day of the week throughout the study.

Number of subjects in period 1	Etanercept	Placebo
Started	11	5
Completed	9	2
Not completed	2	3
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1
Protocol violation	-	1
Study terminated by sponsor	2	-

Period 2

Period 2 title	Period 2 - Open Label
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Period 2 - Open Label Etanercept

Arm description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate 10 to 25 mg once weekly.

Arm type	Active comparator
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Open-label MTX will be administered QW as a single oral dose or in divided doses on the same day.

Number of subjects in period 2	Period 2 - Open Label Etanercept
Started	11
Completed	5
Not completed	6
Study terminated by sponsor	6

Baseline characteristics

Reporting groups

Reporting group title	Period 1, Blinded Treatment

Reporting group description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.

Reporting group values	Period 1, Blinded Treatment	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	54.5		
standard deviation	± 13.43	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	4	4	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analyses set will include all randomized participants who have taken at least one dose of test article.

Subject analysis set title	Period I - Blinded Treatment - Etanercept
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.

Subject analysis set title	Period I - Blinded Treatment - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo injections with oral methotrexate tablets once-weekly.

Reporting group values	Safety Population	Period I - Blinded Treatment - Etanercept	Period I - Blinded Treatment - Placebo
Number of subjects	16	11	5
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	11		
From 65-84 years	5		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	54.6		
standard deviation	± 14.91	±	±
Gender categorical Units: Subjects			
Female	12		
Male	4		

End points

End points reporting groups

Reporting group title	Etanercept
Reporting group description:	
Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo injections with oral methotrexate tablets once-weekly.	
Reporting group title	Period 2 - Open Label Etanercept
Reporting group description:	
Participants received etanercept 50 mg subcutaneously with oral methotrexate 10 to 25 mg once weekly.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analyses set will include all randomized participants who have taken at least one dose of test article.	
Subject analysis set title	Period I - Blinded Treatment - Etanercept
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.	
Subject analysis set title	Period I - Blinded Treatment - Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received placebo injections with oral methotrexate tablets once-weekly.	

Primary: Change from baseline in the disease activity score based on a 28 joint count (DAS28-C-reactive protein [CRP]) at week 12.

End point title	Change from baseline in the disease activity score based on a 28 joint count (DAS28-C-reactive protein [CRP]) at week 12.[1]
End point description:	
DAS28 calculated from the number of swollen joints (SJC) and painful joints (PJC) using the 28 joints count, the c-reactive protein (CRP) and Subject General Health Visual Analogue Scale (VAS) assessment (participant rated health assessment with scores ranging 0 to 100; higher scores indicate worse health status).	
End point type	Primary
End point timeframe:	
Baseline, 12 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was prematurely terminated on 25 June 2014 due to significant and continuing delays in achieving study enrollment. The decision to stop the study was not driven by any safety concerns. At the time of study termination, 20 subjects had been screened, of which 16 subjects were enrolled. No analyses were done due to small numbers of subjects and insufficient data for meaningful statistical analysis available at study termination.

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: participants				

Notes:

[2] - No analyses were done due to insufficient data for meaningful statistical analysis.

[3] - No analyses were done due to insufficient data for meaningful statistical analysis.

[4] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the DAS28 at Week 24

End point title	Change from Baseline in the DAS28 at Week 24

End point description:

DAS28 calculated from the number of SJC and PJC using the 28 joints count, the CRP and Subject General Health VAS assessment (participant rated health assessment with scores ranging 0 to 100; higher scores indicate worse health status).

End point type	Secondary

End point timeframe:

Baseline, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: participants				

Notes:

[5] - No analyses were done due to insufficient data for meaningful statistical analysis.

[6] - No analyses were done due to insufficient data for meaningful statistical analysis.

[7] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with DAS28 <3.2

End point title	Number of Participants with DAS28 <3.2

End point description:

Number of participants with DAS28 <3.2. A score of < 3.2 implied low disease activity.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: participants				

Notes:

[8] - No analyses were done due to insufficient data for meaningful statistical analysis.

[9] - No analyses were done due to insufficient data for meaningful statistical analysis.

[10] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with DAS28 <2.6

End point title	Number of Participants with DAS28 <2.6

End point description:

Number of Participants with DAS28 <2.6. A DAS28 < 2.6 implies remission.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: participants				

Notes:

[11] - No analyses were done due to insufficient data for meaningful statistical analysis.

[12] - No analyses were done due to insufficient data for meaningful statistical analysis.

[13] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving American College of Rheumatology 20% (ACR20) Response

End point title	Number of Participants Achieving American College of Rheumatology 20% (ACR20) Response

End point description:

ACR20 response: greater than or equal to (≥) 20 percent (%) improvement in tender joint count; ≥ 20% improvement in swollen joint count; and ≥ 20% improvement in at least 3 of 5 remaining ACR core measures: participant's assessment of pain; Subject Global Assessment (SGA) of disease activity; Physician Global Assessment (PGA) of disease activity; self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and CRP.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: participants				

Notes:

[14] - No analyses were done due to insufficient data for meaningful statistical analysis.

[15] - No analyses were done due to insufficient data for meaningful statistical analysis.

[16] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving American College of Rheumatology 50% (ACR50) Response

End point title	Number of Participants Achieving American College of Rheumatology 50% (ACR50) Response

End point description:

ACR50 response: greater than or equal to (≥) 50 percent (%) improvement in tender or swollen joint counts and ≥ 50% improvement in 3 of the 5 remaining ACR core measures: participant's assessment of pain; SGA of disease activity; PGA of disease activity; subject's assessment of functional disability via a HAQ; and CRP.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: participants				

Notes:

[17] - No analyses were done due to insufficient data for meaningful statistical analysis.

[18] - No analyses were done due to insufficient data for meaningful statistical analysis.

[19] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving American College of Rheumatology 70% (ACR70) Response

End point title	Number of Participants Achieving American College of Rheumatology 70% (ACR70) Response

End point description:

ACR70 response: greater than or equal to (≥) 70 percent (%) improvement in tender or swollen joint counts and ≥ 70% improvement in 3 of the 5 remaining ACR core measures: participant's assessment of pain; SGA of disease activity; PGA of disease activity; subject's assessment of functional disability via a HAQ; and CRP.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[20]	0[21]	0[22]	
Units: participants				

Notes:

[20] - No analyses were done due to insufficient data for meaningful statistical analysis.

[21] - No analyses were done due to insufficient data for meaningful statistical analysis.

[22] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving American College of Rheumatology 90% (ACR90) Response

End point title	Number of Participants Achieving American College of Rheumatology 90% (ACR90) Response

End point description:

ACR90 response: greater than or equal to (≥) 90 percent (%) improvement in tender or swollen joint counts and ≥ 90% improvement in 3 of the 5 remaining ACR core measures: participant's assessment of pain; SGA of disease activity; PGA of disease activity; subject's assessment of functional disability via a HAQ; and CRP.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[23]	0[24]	0[25]	
Units: participants				

Notes:

[23] - No analyses were done due to insufficient data for meaningful statistical analysis.

[24] - No analyses were done due to insufficient data for meaningful statistical analysis.

[25] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving European League against Rheumatism (EULAR) Good and/or Moderate Response.

End point title	Number of Participants Achieving European League against Rheumatism (EULAR) Good and/or Moderate Response.

End point description:

The Disease Activity Score Based on 28-joints Count based (DAS28-based) EULAR response criteria were used to measure individual response as none, good, and moderate, depending on the extent of change from baseline and the level of disease activity reached. Good responders: change from baseline >1.2 with DAS28 =< 3.2; moderate responders: change from baseline >1.2 with DAS28 >3.2 to =<5.1 or change from baseline >0.6 to =<1.2 with DAS28 =<5.1; non-responders: change from baseline =< 0.6 or change from baseline >0.6 and =<1.2 with DAS28 >5.1.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[26]	0[27]	0[28]	
Units: participants				

Notes:

[26] - No analyses were done due to insufficient data for meaningful statistical analysis.

[27] - No analyses were done due to insufficient data for meaningful statistical analysis.

[28] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving Low Disease Activity or Remission Based on Clinical Disease Activity Index (CDAI)

End point title	Number of Participants Achieving Low Disease Activity or Remission Based on Clinical Disease Activity Index (CDAI)

End point description:

The CDAI is the numerical sum of 4 outcome parameters: tender joint count (TJC) and SJC based on a 28-joint assessment, SGA and PGA assessed on 0-10 point scale; higher scores=greater affliction due to disease activity. CDAI total score = 0-76. CDAI <= 2.8 indicates disease remission, >2.8 to 10 = low disease activity, >10 to 22 = moderate disease activity, and >22 = high disease activity.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	0[30]	0[31]	
Units: participants				

Notes:

[29] - No analyses were done due to insufficient data for meaningful statistical analysis.

[30] - No analyses were done due to insufficient data for meaningful statistical analysis.

[31] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving Low Disease Activity or Remission Based on Simplified Disease Activity Index (SDAI)

End point title	Number of Participants Achieving Low Disease Activity or Remission Based on Simplified Disease Activity Index (SDAI)

End point description:

The SDAI is the numerical sum of five outcome parameters: TJC and SJC based on a 28-joint assessment, SGA and PGA assessed on 0-10 point scale; and CRP (mg/dL). SDAI total score= 0-86. SDAI <=3.3 indicates disease remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high disease activity.

End point type	Secondary

End point timeframe:

12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[32]	0[33]	0[34]	
Units: participants				

Notes:

[32] - No analyses were done due to insufficient data for meaningful statistical analysis.

[33] - No analyses were done due to insufficient data for meaningful statistical analysis.

[34] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CDAI

End point title	Change from Baseline in CDAI

End point description:

Change from Baseline in CDAI scores was to be calculated. The CDAI is the numerical sum of 4 outcome parameters: TJC and SJC based on a 28-joint assessment, SGA and PGA assessed on 0-10 point scale; higher scores=greater affliction due to disease activity. CDAI total score = 0-76. CDAI <= 2.8 indicates disease remission, >2.8 to 10 = low disease activity, >10 to 22 = moderate disease activity, and >22 = high disease activity.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[35]	0[36]	0[37]	
Units: units on a scale				

Notes:

[35] - No analyses were done due to insufficient data for meaningful statistical analysis.

[36] - No analyses were done due to insufficient data for meaningful statistical analysis.

[37] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SDAI

End point title	Change from Baseline in SDAI

End point description:

Change from Baseline in SDAI scores were to be calculated. The SDAI is the numerical sum of five outcome parameters: TJC and SJC based on a 28-joint assessment, SGA and PGA assessed on 0-10 point scale; higher scores=greater affliction due to disease activity, and CRP (mg/dL). SDAI total score= 0-86. SDAI <=3.3 indicates disease remission, >3.4 to 11 = low disease activity, >11 to 26 = moderate disease activity, and >26 = high disease activity.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[38]	0[39]	0[40]	
Units: units on a scale				

Notes:

[38] - No analyses were done due to insufficient data for meaningful statistical analysis.

[39] - No analyses were done due to insufficient data for meaningful statistical analysis.

[40] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Tender/Painful Joints

End point title	Change from Baseline in Number of Tender/Painful Joints

End point description:

Change from Baseline in the number of tender/painful joints using the 28 joint count including

shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees was to be calculated.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[41]	0[42]	0[43]	
Units: number of joints				

Notes:

[41] - No analyses were done due to insufficient data for meaningful statistical analysis.

[42] - No analyses were done due to insufficient data for meaningful statistical analysis.

[43] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Number of Swollen Joints

End point title	Change from Baseline in Number of Swollen Joints

End point description:

Change from Baseline in the number of swollen joints including shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees was to be calculated.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[44]	0[45]	0[46]	
Units: number of swollen joints				

Notes:

[44] - No analyses were done due to insufficient data for meaningful statistical analysis.

[45] - No analyses were done due to insufficient data for meaningful statistical analysis.

[46] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Physician Global Assessment of Disease Activity

End point title	Change from Baseline in Physician Global Assessment of Disease Activity

End point description:

Change from Baseline in the PGA scores was to be estimated. The Study Physician estimated the participant's overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity).

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[47]	0[48]	0[49]	
Units: units on a scale				

Notes:

[47] - No analyses were done due to insufficient data for meaningful statistical analysis.

[48] - No analyses were done due to insufficient data for meaningful statistical analysis.

[49] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject Global Assessment of Disease Activity

End point title	Change from Baseline in Subject Global Assessment of Disease Activity

End point description:

Change from Baseline in Subject Global Assessment of Disease Activity was to be estimated. Participants were to assess their overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity).

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[50]	0[51]	0[52]	
Units: units on a scale				

Notes:

[50] - No analyses were done due to insufficient data for meaningful statistical analysis.

[51] - No analyses were done due to insufficient data for meaningful statistical analysis.

[52] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject Pain

End point title	Change from Baseline in Subject Pain

End point description:

Subject Pain was to be measured on a 0 to 100 mm Visual Analog Scale (VAS), with 0 mm = no pain and 100 mm = most severe pain.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[53]	0[54]	0[55]	
Units: units on a scale				

Notes:

[53] - No analyses were done due to insufficient data for meaningful statistical analysis.

[54] - No analyses were done due to insufficient data for meaningful statistical analysis.

[55] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CRP

End point title	Change from Baseline in CRP

End point description:

The test for CRP is a laboratory measurement for evaluation of an acute phase reactant of inflammation through the use of an ultrasensitive assay. A decrease in the level of CRP indicates reduction in inflammation and therefore improvement.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[56]	0[57]	0[58]	
Units: mg/dL				
number (not applicable)				

Notes:

[56] - No analyses were done due to insufficient data for meaningful statistical analysis.

[57] - No analyses were done due to insufficient data for meaningful statistical analysis.

[58] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Assessment Questionnaire Disability and Discomfort Scales (HAQ-DI)

End point title	Change from Baseline in Health Assessment Questionnaire Disability and Discomfort Scales (HAQ-DI)

End point description:

Health Assessment Questionnaire-Disability Index (HAQ-DI): participant-reported assessment of ability to perform tasks in 8 categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[59]	0[60]	0[61]	
Units: units on a scale				

Notes:

[59] - No analyses were done due to insufficient data for meaningful statistical analysis.

[60] - No analyses were done due to insufficient data for meaningful statistical analysis.

[61] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Euro Quality of Life (Qol) EQ-5 Dimensions Questionnaire (EQ-5D)

End point title	Change from Baseline in Euro Quality of Life (Qol) EQ-5 Dimensions Questionnaire (EQ-5D)

End point description:

The EuroQol-5 Dimensions (EQ-5D) is a participant-completed questionnaire designed to assess health related quality of life involving 2 components: a Health State Profile and a VAS. For the Health State Profile, participants recorded their level of current health for 5 domains comprising a health profile: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores from the 5 domains may be used to calculate a single index value, also known as a utility score. On the VAS participants were asked to rate their current health on a scale from 0 to 100 mm, where 0 represented the "worst imaginable health state" and 100 represented the "best imaginable health state."

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[62]	0[63]	0[64]	
Units: units on a scale				

Notes:

[62] - No analyses were done due to insufficient data for meaningful statistical analysis.

[63] - No analyses were done due to insufficient data for meaningful statistical analysis.

[64] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Short Form-36 Health Survey (SF-36)

End point title	Change from Baseline in Short Form-36 Health Survey (SF-36)

End point description:

The 36-Item Short Form Health Survey (SF-36) is widely used 36-item questionnaire that measures general health-related quality of life in the following 8 domains: physical function, role limitations due to physical health, bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems, and mental health. Scores for the 8 domains range from 0 to 100 where higher scores are better.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[65]	0[66]	0[67]	
Units: units on a scale				

Notes:

[65] - No analyses were done due to insufficient data for meaningful statistical analysis.

[66] - No analyses were done due to insufficient data for meaningful statistical analysis.

[67] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Vectra disease activity levels

End point title	Change from Baseline in Vectra disease activity levels

End point description:

The change from Baseline in Vectra disease activity levels was to be estimated. The assessment measures serum protein biomarkers associated with RA. It has a range from 1-100 with lower scores indicating the better outcome.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[68]	0[69]	0[70]	
Units: units on a scale				

Notes:

[68] - Vectra disease activity analysis of laboratory samples was not conducted due to study termination.
[69] - Vectra disease activity analysis of laboratory samples was not conducted due to study termination.
[70] - Vectra disease activity analysis of laboratory samples was not conducted due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient Acceptable Symptom State (PASS)

End point title	Change from Baseline in Patient Acceptable Symptom State (PASS)

End point description:

The Patient Acceptable Symptom State (PASS) was a participant-completed form in which participants were asked to "Think about all the ways your rheumatoid arthritis (RA) has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable or unacceptable to you?" The participant indicated a response of either "acceptable" or "unacceptable".

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[71]	0[72]	0[73]	
Units: units on a scale				

Notes:

[71] - No analyses were done due to insufficient data for meaningful statistical analysis.

[72] - No analyses were done due to insufficient data for meaningful statistical analysis.

[73] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Positive Etanercept Anti-drug Antibody Status

End point title	Number of Participants with Positive Etanercept Anti-drug Antibody Status

End point description:

Blood samples (6 mL) were collected at the baseline, Week 12, and Week 24 visits, or upon early withdrawal, to provide a minimum of 1 mL serum each for ETN ADA and ETN neutralizing antibody analyses. Samples which were positive for ETN antidrug antibodies were then also tested for ETN neutralizing antibodies.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[74]	0[75]	0[76]	
Units: participants				

Notes:

[74] - No analyses were done due to insufficient data for meaningful statistical analysis.

[75] - No analyses were done due to insufficient data for meaningful statistical analysis.

[76] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Positive Etanercept Neutralizing Anti-drug Antibody Status

End point title	Number of Participants with Positive Etanercept Neutralizing Anti-drug Antibody Status

End point description:

Blood samples (6 mL) were collected at the baseline, Week 12, and Week 24 visits, or upon early withdrawal, to provide a minimum of 1 mL serum each for ETN ADA and ETN neutralizing antibody analyses. Samples which were positive for ETN antidrug antibodies were then also tested for ETN neutralizing antibodies.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[77]	0[78]	0[79]	
Units: participants				

Notes:

[77] - No analyses were done due to insufficient data for meaningful statistical analysis.

[78] - No analyses were done due to insufficient data for meaningful statistical analysis.

[79] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject General Health VAS.

End point title	Change from Baseline in Subject General Health VAS.

End point description:

Subject General Health VAS assessment (participant rated health assessment with scores ranging 0 to 100; higher scores indicate worse health status).

End point type	Secondary

End point timeframe:

Baseline, 12 weeks, 24 weeks

End point values	Etanercept	Placebo	Period 2 - Open Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[80]	0[81]	0[82]	
Units: units on a scale				

Notes:

[80] - No analyses were done due to insufficient data for meaningful statistical analysis.

[81] - No analyses were done due to insufficient data for meaningful statistical analysis.

[82] - No analyses were done due to insufficient data for meaningful statistical analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day the first dose of the investigational product was administered up to 28 days after last dose was administered

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one participant and as non-serious in another participant, or one participant may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Period I - Blinded Treatment - Etanercept

Reporting group description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate tablets once-weekly.

Reporting group title	Period I - Blinded Treatment - Placebo

Reporting group description:

Participants received placebo injections with oral methotrexate tablets once-weekly.

Reporting group title	Period 2 - Open-Label - Etanercept

Reporting group description:

Participants received etanercept 50 mg subcutaneously with oral methotrexate 10 to 25 mg once weekly.

Serious adverse events	Period I - Blinded Treatment - Etanercept	Period I - Blinded Treatment - Placebo	Period 2 - Open-Label - Etanercept
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Period I - Blinded Treatment - Etanercept	Period I - Blinded Treatment - Placebo	Period 2 - Open-Label - Etanercept
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	3 / 5 (60.00%)	4 / 11 (36.36%)
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Injection site reaction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 11 (18.18%)	0 / 5 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			

Tendonitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 5 (20.00%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Tooth infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 5 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 5 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	Key substantial amendments: 2. STUDY OBJECTIVES AND ENDPOINTS: added ETN ADA status and neutralizing antibody (NA) status as secondary endpoints. 3. STUDY DESIGN: reduced sample size; add an interim analysis after 30 mAb ADA+ subjects have either withdrawn prior to or completed Period 1; added that sample size may be increased based on the results of interim analysis; clarify that enrollment into study will not be stopped while interim analysis is prepared. 4.2. EXCLUSION CRITERIA: revised latent tuberculosis (TB) criteria and added criteria for testing of ALT and AST in subjects receiving TB chemoprophylaxis between screening and baseline visits. 5. STUDY TREATMENTS: revised planned number of subjects. 5.5.3. OTHER PERMITTED TREATMENTS: allowed chemoprophylaxis for latent TB to be started between screening and baseline visits. 6.1. SCREENING: added details on PPD test; clarifed that high-sensitivity CRP will be used . 6.2. BASELINE VISIT, 6.3. TREATMENT PERIOD – WEEK 4 TO WEEK 24 VISITS and 6.4. EARLY WITHDRAWAL VISIT: added testing for ETN ADA status, NA, and drug levels. 7.5.2. SERUM FOR PHARMACOKINETIC ANALYSIS OF ETN: added section to describe collection and analysis of samples for ETN concentrations. 7.5.4. SERUM FOR ANALYSIS OF ETN ADA AND ETN NEUTRALIZING ANTIBODIES: added section to describe collection and analysis of samples for ETN ADAs and NA. 7.5.6. PHARMACOKINETIC/PHARMACODYNAMICS (PK/PD): revisions made to the ETN concentrations; an analysis plan for infliximab, adalimumab, and ETN drug concentrations. 8.2. REPORTING PERIOD; 8.3. DEFINITION OF AN ADVERSE EVENT: modify safety monitoring procedures 9.1. SAMPLE SIZE DETERMINATION: use simulation approach for sample size calculation, revise power and number of subjects. 9.2.1. ANALYSIS OF PRIMARY ENDPOINT; 9.2.2 ANALYSIS OF SECONDARY ENDPOINT: changes to the statistical methods. 9.6.2. SAMPLE SIZE REESTIMATION: added information regarding interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 June 2014	This study was prematurely terminated on 25 June 2014 due to significant and continuing delays in achieving study enrollment. The decision to stop the study was not driven by any safety concerns.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No analyses were done due to small numbers of subjects and insufficient data for meaningful statistical analysis available at study termination.

Notes: