Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF THE MAINTENANCE OF EFFICACY OF ETANERCEPT PLUS DMARD(S) COMPARED WITH DMARD(S) ALONE IN SUBJECTS WITH RHEUMATOID ARTHRITIS AFTER ACHIEVING AN ADEQUATE RESPONSE WITH ETANERCEPT PLUS DMARD(S).

Summary

EudraCT number	2011-005448-87
Trial protocol	HU CZ
Global end of trial date	27 March 2015

Results information

Result version number	v1 (current)
This version publication date	12 March 2016
First version publication date	12 March 2016

Trial information

Trial identification

Sponsor protocol code	B1801315

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01578850
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street,, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 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	16 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2015
Global end of trial reached?	Yes
Global end of trial date	27 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the maintenance of efficacy of the combination of ETN 50 mg once weekly plus MTX (±other DMARDs) therapy with that of MTX (±other DMARDs) at Week 52 in participants with moderately to severely active RA who have achieved LDA (DAS28-ESR<3.2) after 24 weeks of therapy with open-label ETN 50 mg once weekly plus MTX (±other DMARDs) in a treat to target paradigm. An adequate response is defined as a DAS28<3.2 at Week 24.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences [CIOMS] 2002), Guidelines for GCP (International Conference on Harmonisation [ICH] 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2012
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	Brazil: 18
Country: Number of subjects enrolled	China: 29
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Czech Republic: 50
Country: Number of subjects enrolled	Egypt: 41
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Jordan: 1
Country: Number of subjects enrolled	Lebanon: 1
Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Mexico: 53
Country: Number of subjects enrolled	Philippines: 35
Country: Number of subjects enrolled	Qatar: 2
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	South Africa: 30
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Thailand: 34
Country: Number of subjects enrolled	Ukraine: 58

Country: Number of subjects enrolled	United Arab Emirates: 4
Country: Number of subjects enrolled	Russian Federation: 61
Worldwide total number of subjects	489
EEA total number of subjects	72

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)	452
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study consisted of Period 1 (an open-label, 24-week treat-to-target period), and Period 2 (a double-blind, randomized, 28-week period for participants who qualified for randomization).

Pre-assignment

Screening details:

The study was conducted in participants with rheumatoid arthritis (RA) who had moderate to severe disease activity despite methotrexate (MTX) therapy (≥10 mg/week) with or without other non-biologic disease modifying anti-rheumatic drugs (DMARDs) for at least 12 weeks prior to screening.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Study medication was not blinded during the open-label (period 1).

Arms

Arm title	Open-Label Treatment

Arm description:

Participants in open-label treatment received Etanercept (ETN) 50 milligram (mg) once a week (QW) with MTX (with or without other DMARDs).

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants in open-label treatment received ETN 50 mg QW with MTX (with or without other DMARDs).

Number of subjects in period 1	Open-Label Treatment
Started	489
Completed	452
Not completed	37
Adverse event, serious fatal	1
Does Not Meet Entrance Criteria	12
Consent withdrawn by subject	9
Adverse event, non-fatal	11
Insufficient Clinical Response	1
Study Terminated by Sponsor	3

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

The method was an electronic process. Blinding codes were only to be broken in emergency situations for reasons of participant safety.

Arms

Are arms mutually exclusive?	No
Arm title	Etanercept

Arm description:

Participants were randomized to receive ETN 50 mg QW with MTX (with or without other DMARDs).

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

Dosage and administration details:

Participants were randomized to receive ETN 50 mg QW with MTX (with or without other DMARDs).

Arm title	Placebo

Arm description:

Participants were randomized to receive PBO 50 mg QW + MTX (with or without DMARDs).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants were randomized to receive PBO 50 mg QW with MTX (with or without other DMARDs).

Number of subjects in period 2	Etanercept	Placebo
Started	167	176
Completed	154	162
Not completed	13	14
Consent withdrawn by subject	2	2
Adverse event, non-fatal	3	6
Insufficient Clinical Response	1	-
Unspecified Reasons	1	-

Study Terminated by Sponsor	5	4
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Open-Label Treatment
Reporting group description:	
Participants in open-label treatment received Etanercept (ETN) 50 milligram (mg) once a week (QW) with MTX (with or without other DMARDs).	

Reporting group values	Open-Label Treatment	Total	
Number of subjects	489	489	
Age categorical Units: Subjects			
Adults (18-64 years)	452	452	
From 65-84 years	37	37	
Age Continuous | Units: Years			
arithmetic mean	47.5		
standard deviation	± 12.24	-	
Gender, Male/Female Units: Participants			
Male	423	423	
Female	66	66	

End points

End points reporting groups	
Reporting group title	Open-Label Treatment
Reporting group description:	
Participants in open-label treatment received Etanercept (ETN) 50 milligram (mg) once a week (QW) with MTX (with or without other DMARDs).	
Reporting group title	Etanercept
Reporting group description:	
Participants were randomized to receive ETN 50 mg QW with MTX (with or without other DMARDs).	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive PBO 50 mg QW + MTX (with or without DMARDs).	

Primary: Proportion of participants who remained in Low Disease Activity (LDA) (Disease Activity Score in 28 joints-erythrocyte sedimentation rate [DAS28-ESR] <3.2) at Week 52.

End point title	Proportion of participants who remained in Low Disease Activity (LDA) (Disease Activity Score in 28 joints-erythrocyte sedimentation rate [DAS28-ESR] <3.2) at Week 52.
End point description:	
Proportion of participants who remained in LDA DAS28-ESR <3.2 at Week 52 is presented below.	
End point type	Primary
End point timeframe:	
Baseline and Week 52	

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: percentage of participants				
number (not applicable)	43.6	17.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	26.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.78
upper limit	35.81

Notes:

[1] - Participants who flared in Period 2 are retreated and the data included used in efficacy analyses were carried forward from the last visit before retreatment.

Secondary: Proportion of participants who remained in Remission at Week 52 (DAS28-ESR)

End point title	Proportion of participants who remained in Remission at Week 52 (DAS28-ESR)

End point description:

Proportion of participants who remained in Remission (DAS28-ESR <2.6) at Week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)	53.2	29.5		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.83
upper limit	40.61

Secondary: Proportion of participants achieving LDA (DAS28-ESR and DAS28-C-reactive protein [CRP]) at each visit during Period 1

End point title	Proportion of participants achieving LDA (DAS28-ESR and

	DAS28-C-reactive protein [CRP]) at each visit during Period 1

End point description:

Proportion of participants who achieved LDA (DAS28-ESR and DAS28-CRP at each visit during period 1 is presented below.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: Percentage of participants				
number (not applicable)				
DAS28-ESR Week 4 (N= 473)	9.5			
DAS28-CRP Week 4 (N= 465)	20.6			
DAS28-ESR Week 8 (N= 473)	20.3			
DAS28-CRP Week 8 (N= 471)	34.6			
DAS28-ESR Week 16 (N= 473)	32.8			
DAS28-CRP Week 16 (N= 472)	52.8			
DAS28-ESR Week 24 (N= 473)	72.1			
DAS28-CRP Week 24 (N= 472)	72.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving LDA (DAS28-ESR and DAS28-CRP) at each visit during Period 2

End point title	Proportion of participants achieving LDA (DAS28-ESR and DAS28-CRP) at each visit during Period 2

End point description:

Proportion of participants who achieved LDA (DAS28-ESR and DAS28-CRP at each visit during period 2 is presented below.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)				
DAS28-ESR Baseline (N= 163, 168)	0	0.6		
DAS28-CRP Baseline (N= 163, 168)	0.6	0		

DAS28-ESR Week 24 (N= 163, 168)	100	100		
DAS28-CRP Week 24 (N= 163, 168)	87.7	85.1		
DAS28-ESR Week 28 (N= 163, 168)	62.6	41.1		
DAS28-CRP Week 28 (N= 160, 166)	74.4	55.4		
DAS28-ESR Week 36 (N= 163, 168)	55.2	24.4		
DAS28-CRP Week 36 (N= 162, 167)	69.1	41.9		
DAS28-ESR Week 44 (N= 163, 168)	51.5	20.2		
DAS28-CRP Week 44 (N= 162, 167)	69.1	38.9		
DAS28-ESR Week 52 (N= 163, 168)	43.6	17.3		
DAS28-CRP Week 52 (N= 162, 167)	64.2	37.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: DAS28-ESR Baseline	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	0.57

Statistical analysis title	Statistical analysis 2
Statistical analysis description: DAS28-CRP Baseline	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	1.81

Statistical analysis title	Statistical analysis 3
Statistical analysis description: DAS28-CRP Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.76
upper limit	9.98

Statistical analysis title	Statistical analysis 4
Statistical analysis description: DAS28-ESR Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.99
upper limit	32.02

Statistical analysis title	Statistical analysis 5
Statistical analysis description: DAS28-CRP Week 28	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.81
upper limit	29.1

Statistical analysis title	Statistical analysis 6
Statistical analysis description: DAS28-ESR Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	30.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.79
upper limit	40.83

Statistical analysis title	Statistical analysis 7
Statistical analysis description: DAS28-CRP Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.89
upper limit	37.54

Statistical analysis title	Statistical analysis 8
Statistical analysis description: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	31.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.51
upper limit	41.08

Statistical analysis title	Statistical analysis 9
Statistical analysis description: DAS28-CRP Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.95
upper limit	40.47

Statistical analysis title	Statistical analysis 10
Statistical analysis description: DAS28-ESR Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.78
upper limit	35.81

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
DAS28-CRP Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.67
upper limit	37.47

Secondary: Proportion of participants achieving remission (DAS28-ESR and DAS28-CRP) at each visit during Period 1

End point title	Proportion of participants achieving remission (DAS28-ESR and DAS28-CRP) at each visit during Period 1
End point description:	
Proportion of participants who achieved remission (DAS28-ESR and DAS28-CRP at each visit during period 1 is presented below.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 4, 8, 16 and 24	

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: Percentage of participants				
number (not applicable)				
DAS28-ESR Week 4 (N= 473)	4			
DAS28-CRP Week 4 (N= 465)	9			
DAS28-ESR Week 8 (N= 473)	8.9			
DAS28-CRP Week 8 (N= 471)	17.8			
DAS28-ESR Week 16 (N= 473)	13.5			
DAS28-CRP Week 16 (N= 472)	31.1			
DAS28-ESR Week 24 (N= 473)	26.6			
DAS28-CRP Week 24 (N= 472)	49.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving remission (DAS28-ESR and DAS28-CRP) at each visit during Period 2

End point title	Proportion of participants achieving remission (DAS28-ESR and DAS28-CRP) at each visit during Period 2

End point description:

Proportion of participants who achieved LDA (DAS28-ESR and DAS28-CRP at each visit during period 2 is presented below.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)				
DAS28-ESR Baseline (N= 163, 168)	0	0		
DAS28-CRP Baseline (N= 163, 168)	0	0		
DAS28-ESR Week 24 (N= 163, 168)	38	36.3		
DAS28-CRP Week 24 (N= 163, 168)	64.4	63.1		
DAS28-ESR Week 28 (N= 163, 168)	32.5	20.2		
DAS28-CRP Week 28 (N= 160, 166)	51.9	34.9		
DAS28-ESR Week 36 (N= 163, 168)	31.9	17.3		
DAS28-CRP Week 36 (N= 162, 167)	50	25.1		
DAS28-ESR Week 44 (N= 163, 168)	30.7	11.9		
DAS28-CRP Week 44 (N= 162, 167)	51.9	21		
DAS28-ESR Week 52 (N= 163, 168)	33.7	13.1		
DAS28-CRP Week 52 (N= 162, 167)	46.9	19.8		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: DAS28-CRP Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.774
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.03
upper limit	11.68

Statistical analysis title	Statistical analysis 2
Statistical analysis description: DAS28-ESR Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	21.69

Statistical analysis title	Statistical analysis 3
Statistical analysis description: DAS28-CRP Week 28	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	16.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.33
upper limit	27.54

Statistical analysis title	Statistical analysis 4
Statistical analysis description: DAS28-ESR Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.48
upper limit	23.8

Statistical analysis title	Statistical analysis 5
Statistical analysis description: DAS28-CRP Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.72
upper limit	34.98

Statistical analysis title	Statistical analysis 6
Statistical analysis description: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	18.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.16
upper limit	27.38

Statistical analysis title	Statistical analysis 7
Statistical analysis description: DAS28-CRP Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.03
upper limit	40.76

Statistical analysis title	Statistical analysis 8
Statistical analysis description: DAS28-ESR Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	20.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.78
upper limit	29.52

Statistical analysis title	Statistical analysis 9
Statistical analysis description: DAS28-CRP Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.38
upper limit	36.93

Secondary: Change from Baseline in DAS28-CRP and DAS28-ESR in Period 1

End point title	Change from Baseline in DAS28-CRP and DAS28-ESR in Period 1

End point description:

The DAS assessment is a derived measurement with differential weight given to each component. The DAS28-ESR and DAS28-CRP was calculated at every visit within the clinical database in period 1. The components of the DAS28 ESR score assessment are: Tender/ Painful Joint Count (28), Swollen Joint Count (28); ESR, Subject General Health VAS assessment. The components of the DAS28 CRP score assessment were: Tender/Painful Joint Count (28); Swollen Joint Count (28), hsCRP, and the Subject General Health VAS assessment. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
DAS28-ESR Week 4 (N= 473)	-1.61 (± 1.08)			
DAS28-CRP Week 4 (N= 465)	-1.61 (± 1.05)			
DAS28-ESR Week 8 (N= 473)	-2.14 (± 1.18)			
DAS28-CRP Week 8 (N= 471)	-2.09 (± 1.14)			
DAS28-ESR Week 16 (N= 473)	-2.62 (± 1.26)			
DAS28-CRP Week 16 (N= 472)	-2.54 (± 1.21)			
DAS28-ESR Week 24 (N= 473)	-3.23 (± 1.35)			
DAS28-CRP Week 24 (N= 472)	-2.95 (± 1.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-CRP and DAS28-ESR in Period 2

End point title	Change from Baseline in DAS28-CRP and DAS28-ESR in Period 2

End point description:

The DAS assessment is a derived measurement with differential weight given to each component. The DAS28-ESR and DAS28-CRP was calculated at every visit within the clinical database in period 2. The components of the DAS28 ESR score assessment are: Tender/ Painful Joint Count (28), Swollen Joint Count (28); ESR, Subject General Health VAS assessment. The components of the DAS28 CRP score assessment were: Tender/Painful Joint Count (28); Swollen Joint Count (28), hsCRP, and the Subject General Health VAS assessment. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
DAS28-ESR Week 24 (N= 163, 168)	-3.79 (± 1.04)	-3.7 (± 0.99)		
DAS28-CRP Week 24 (N= 163, 168)	-3.36 (± 1.03)	-3.32 (± 1.05)		
DAS28-ESR Week 28 (N= 163, 168)	-3.35 (± 1.31)	-2.73 (± 1.43)		
DAS28-CRP Week 28 (N= 160, 166)	-3.06 (± 1.26)	-2.53 (± 1.4)		
DAS28-ESR Week 36 (N= 163, 168)	-3.2 (± 1.4)	-2.4 (± 1.49)		
DAS28-CRP Week 36 (N= 162, 167)	-2.97 (± 1.35)	-2.27 (± 1.48)		
DAS28-ESR Week 44 (N= 163, 168)	-3.15 (± 1.36)	-2.31 (± 1.49)		
DAS28-CRP Week 44 (N= 162, 167)	-2.95 (± 1.35)	-2.19 (± 1.5)		
DAS28-ESR Week 52 (N= 163, 168)	-3.08 (± 1.4)	-2.28 (± 1.46)		
DAS28-CRP Week 52 (N= 162, 167)	-2.92 (± 1.36)	-2.16 (± 1.45)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: DAS28-ESR Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	-0.2

Statistical analysis title	Statistical analysis 2
Statistical analysis description: DAS28-CRP Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	-0.11

Statistical analysis title	Statistical analysis 3
Statistical analysis description: DAS28-ESR Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.39

Statistical analysis title	Statistical analysis 4
Statistical analysis description: DAS28-CRP Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.28

Statistical analysis title	Statistical analysis 5
Statistical analysis description: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.46

Statistical analysis title	Statistical analysis 6
Statistical analysis description: DAS28-CRP Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	-0.37

Statistical analysis title	Statistical analysis 7
Statistical analysis description: DAS28-ESR Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	-0.4

Statistical analysis title	Statistical analysis 8
Statistical analysis description: DAS28-CRP Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.36

Secondary: Time-to-flare during Period 2, based on the protocol criteria

End point title	Time-to-flare during Period 2, based on the protocol criteria
End point description: Flare is defined as the criteria of loss of LDA plus ≥0.6 unit worsening in DAS28 score during period 2.	
End point type	Secondary
End point timeframe: Baseline and Week 52	

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)	52.1	79.8		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Proportion of participants achieving European League Against Rheumatism (EULAR) good and or moderate responses (by both DAS28-ESR and DAS28-CRP scores) at each visit during Period 1.

End point title	Proportion of participants achieving European League Against

	Rheumatism (EULAR) good and or moderate responses (by both DAS28-ESR and DAS28-CRP scores) at each visit during Period 1.

End point description:

EULAR response is based on DAS28-ESR scores. The following good and moderate response is defined based on DAS28-ESR at endpoint (DAS28-ESR improvement at from Baseline in parenthesis): ≤3.2 units (>1.2 units) is good response; ≤3.2 units (0.6-1.2 units) are moderate response; ≤3.2 units (≤0.6 units) are no response.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: Percentage of participants				
number (not applicable)				
Good Response: DAS28-ESR Week 4 (N= 473)	9.5			
Good Response: DAS28-CRP Week 4 (N= 465)	18.9			
Good Response: DAS28-ESR Week 8 (N= 473)	19.5			
Good Response: DAS28-CRP Week 8 (N= 471)	33.5			
Good Response: DAS28-ESR Week 16 (N= 473)	32.3			
Good Response: DAS28-CRP Week 16 (N= 472)	51.9			
Good Response: DAS28-ESR Week 24 (N= 473)	71.5			
Good Response: DAS28-CRP Week 24 (N= 472)	71.4			
Moderate Response: DAS28-ESR Week 4 (N= 473)	69.1			
Moderate Response: DAS28-CRP Week 4 (N= 465)	79.8			
Moderate Response: DAS28-ESR Week 8 (N= 473)	86.9			
Moderate Response: DAS28-CRP Week 8 (N= 471)	87.5			
Moderate Response: DAS28-ESR Week 16 (N= 473)	92			
Moderate Response: DAS28-CRP Week 16 (N= 472)	92.8			
Moderate Response: DAS28-ESR Week 24 (N= 473)	94.1			
Moderate Response: DAS28-CRP Week 24 (N= 472)	95.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving EULAR good and or moderate responses (by both DAS28-ESR and DAS28-CRP scores) at each visit during Period 2.

End point title	Proportion of participants achieving EULAR good and or moderate responses (by both DAS28-ESR and DAS28-CRP scores) at each visit during Period 2.

End point description:

EULAR response is based on DAS28-ESR scores. The following good and moderate response is defined based on DAS28-ESR at endpoint (DAS28-ESR improvement at from Baseline in parenthesis): ≤3.2 units (>1.2 units) is good response; ≤3.2 units (0.6-1.2 units) are moderate response; ≤3.2 units (≤0.6 units) are no response.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)				
Good Response: DAS28-ESR Week 24 (N= 163, 168)	99.4	99.4		
Good Response: DAS28-CRP Week 24 (N= 163, 168)	86.5	85.1		
Good Response: DAS28-ESR Week 28 (N= 163, 168)	62.6	41.1		
Good Response: DAS28-CRP Week 28 (N= 160, 166)	73.1	54.8		
Good Response: DAS28-ESR Week 36 (N= 163, 168)	55.2	23.8		
Good Response: DAS28-CRP Week 36 (N= 162, 167)	67.9	40.7		
Good Response: DAS28-ESR Week 44 (N= 163, 168)	50.9	19.6		
Good Response: DAS28-CRP Week 44 (N= 162, 167)	68.5	37.7		
Good Response: DAS28-ESR Week 52 (N= 163, 168)	42.9	16.7		
Good Response: DAS28-CRP Week 52 (N= 162, 167)	63	35.9		
Moderate Response: DAS28-ESR Week 24 (N= 163,168)	100	100		
Moderate Response: DAS28-CRP Week 24 (N= 163,168)	100	100		
Moderate Response: DAS28-ESR Week 28 (N= 163,168)	95.7	87.5		
Moderate Response: DAS28-CRP Week 28 (N= 160,166)	96.9	90.4		
Moderate Response: DAS28-ESR Week 36 (N= 163,168)	93.9	83.9		
Moderate Response: DAS28-CRP Week 36 (N= 162,167)	94.4	85.6		

Moderate Response: DAS28-ESR Week 44 (N= 163,168)	93.3	81.5		
Moderate Response: DAS28-CRP Week 44 (N= 162,167)	95.1	84.4		
Moderate Response: DAS28-ESR Week 52 (N= 163,168)	93.3	82.1		
Moderate Response: DAS28-CRP Week 52 (N= 162,167)	95.7	84.4		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Good Response: DAS28-CRP Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.961
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.13
upper limit	8.9

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Good Response: DAS28-ESR Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	21.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.99
upper limit	32.02

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Good Response: DAS28-CRP Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.08
upper limit	28.53

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Good Response: DAS28-ESR Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	31.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.42
upper limit	41.39

Statistical analysis title	Statistical analysis 5
Statistical analysis description: Good Response: DAS28-CRP Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.83
upper limit	37.54

Statistical analysis title	Statistical analysis 6
Statistical analysis description: Good Response: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	31.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.53
upper limit	41.02

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Good Response: DAS28-CRP Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	30.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.54
upper limit	41.05

Statistical analysis title	Statistical analysis 8
Statistical analysis description: Good Response: DAS28-ESR Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	26.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.82
upper limit	35.74

Statistical analysis title	Statistical analysis 9
Statistical analysis description: Good Response: DAS28-CRP Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.63
upper limit	37.44

Statistical analysis title	Statistical analysis 10
Statistical analysis description: Good Response: DAS28-ESR Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.766
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	1.65

Statistical analysis title	Statistical analysis 11
Statistical analysis description: Moderate Response: DAS28-ESR Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.32
upper limit	14.1

Statistical analysis title	Statistical analysis 12
Statistical analysis description: Moderate Response: DAS28-CRP Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	11.75

Statistical analysis title	Statistical analysis 13
Statistical analysis description: Moderate Response: DAS28-ESR Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.27
upper limit	16.6

Statistical analysis title	Statistical analysis 14
Statistical analysis description: Moderate Response: DAS28-CRP Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.43
upper limit	15.2

Statistical analysis title	Statistical analysis 15
Statistical analysis description: Moderate Response: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.69
upper limit	18.72

Statistical analysis title	Statistical analysis 16
Statistical analysis description: Moderate Response: DAS28-ESR Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	10.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	17.06

Statistical analysis title	Statistical analysis 17
Statistical analysis description: Moderate Response: DAS28-ESR Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.15
upper limit	18.06

Statistical analysis title	Statistical analysis 18
Statistical analysis description: Moderate Response: DAS28-CRP Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.92
upper limit	17.58

Secondary: Proportion of participants achieving LDA or remission based on Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) at each visit during Period 1.

End point title	Proportion of participants achieving LDA or remission based on Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) at each visit during Period 1.

End point description:

SDAI and CDAI are defined as: 1) SDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0-28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) + hs CRP (in mg/dL) in Period 1. 2) CDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0 28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) in Period 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: Percentage of participants				
number (not applicable)				
CDAI: LDA Baseline (N= 478)	0.4			
CDAI: LDA Week 4 (N= 473)	16.7			
CDAI: LDA Week 8 (N= 473)	33.8			
CDAI: LDA Week 16 (N= 473)	53.9			
CDAI: LDA Week 24 (N= 473)	75.7			
CDAI: Remission: Baseline (N= 478)	0			
CDAI: Remission: Week 4 (N= 473)	0.4			
CDAI: Remission: Week 8 (N= 473)	1.7			
CDAI: Remission: Week 16 (N= 473)	6.1			
CDAI: Remission: Week 24 (N= 473)	10.8			
SDAI: LDA: Baseline (N= 478)	0.2			
SDAI: LDA: Week 4 (N= 465)	16.1			
SDAI: LDA: Week 8 (N= 471)	32.5			
SDAI: LDA: Week 16 (N= 472)	52.3			

SDAI: LDA: Week 24 (N= 472)	72.5			
SDAI: Remission: Baseline (N= 478)	0			
SDAI: Remission: Week 4 (N= 465)	0.6			
SDAI: Remission: Week 8 (N= 471)	1.9			
SDAI: Remission: Week 16 (N= 472)	6.8			
SDAI: Remission: Week 24 (N= 472)	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving LDA or remission based on CDAI and SDAI at each visit during Period 2.

End point title	Proportion of participants achieving LDA or remission based on CDAI and SDAI at each visit during Period 2.

End point description:

SDAI and CDAI are defined as: 1) SDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0-28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) + hs CRP (in mg/dL) in Period 2. 2) CDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0 28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) in Period 2.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)				
CDAI: LDA Baseline (N= 163, 168)	0.6	0		
CDAI: LDA Week 24 (N= 163, 168)	93.9	90.5		
CDAI: LDA Week 28 (N= 163, 168)	76.1	57.7		
CDAI: LDA Week 36 (N= 163, 168)	71.2	47		
CDAI: LDA Week 44 (N= 163, 168)	70.6	43.5		
CDAI: LDA Week 52 (N= 163, 168)	66.9	42.9		
CDAI: Remission: Baseline (N= 163, 168)	0	0		
CDAI: Remission: Week 24 (N= 163, 168)	16.6	14.3		
CDAI: Remission: Week 28 (N= 163, 168)	14.7	14.3		
CDAI: Remission: Week 36 (N= 163, 168)	20.9	12.5		
CDAI: Remission: Week 44 (N= 163, 168)	22.1	12.5		
CDAI: Remission: Week 52 (N= 163, 168)	20.9	11.9		
SDAI: LDA: Baseline (N= 163, 168)	0.6	0		
SDAI: LDA: Week 24 (N= 163, 168)	90.2	86.9		

SDAI: LDA: Week 28 (N= 160, 166)	73.1	55.4		
SDAI: LDA: Week 36 (N= 162, 167)	69.8	55.4		
SDAI: LDA: Week 44 (N= 162, 167)	69.8	42.5		
SDAI: LDA: Week 52 (N= 162, 167)	66.7	42.5		
SDAI: Remission: Baseline (N= 163, 168)	0	0		
SDAI: Remission: Week 24 (N= 163, 168)	20.9	17.9		
SDAI: Remission: Week 28 (N= 160, 166)	16.3	16.3		
SDAI: Remission: Week 36 (N= 162, 167)	22.8	12.6		
SDAI: Remission: Week 44 (N= 162, 167)	22.2	13.2		
SDAI: Remission: Week 52 (N= 162, 167)	25.3	13.2		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: CDAI: LDA Baseline	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	1.81

Statistical analysis title	Statistical analysis 2
Statistical analysis description: CDAI: LDA: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.341
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	3.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.38
upper limit	9.16

Statistical analysis title	Statistical analysis 3
Statistical analysis description: CDAI: LDA: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.4
upper limit	28.27

Statistical analysis title	Statistical analysis 4
Statistical analysis description: CDAI: LDA: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.88
upper limit	34.4

Statistical analysis title	Statistical analysis 5
Statistical analysis description: CDAI: LDA: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.85
upper limit	37.35

Statistical analysis title	Statistical analysis 6
Statistical analysis description: CDAI: LDA: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.61
upper limit	34.42

Statistical analysis title	Statistical analysis 7
Statistical analysis description: CDAI: Remission: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.774
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	10.06

Statistical analysis title	Statistical analysis 8
Statistical analysis description: CDAI: Remission: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.645
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.15
upper limit	8.03

Statistical analysis title	Statistical analysis 9
Statistical analysis description: CDAI: Remission: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	16.35

Statistical analysis title	Statistical analysis 10
Statistical analysis description: CDAI: Remission: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	17.68

Statistical analysis title	Statistical analysis 11
Statistical analysis description: CDAI: Remission: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	16.88

Statistical analysis title	Statistical analysis 12
Statistical analysis description: SDAI: LDA: Baseline	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.358
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	1.81

Statistical analysis title	Statistical analysis 13
Statistical analysis description: SDAI: LDA: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.258
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.57
upper limit	10.13

Statistical analysis title	Statistical analysis 14
Statistical analysis description: SDAI: LDA: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.49
upper limit	27.92

Statistical analysis title	Statistical analysis 15
Statistical analysis description: SDAI: LDA: Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	27.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.93
upper limit	37.55

Statistical analysis title	Statistical analysis 16
Statistical analysis description: SDAI: LDA: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.83
upper limit	42.23

Statistical analysis title	Statistical analysis 17
Statistical analysis description: SDAI: LDA: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	28.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	18
upper limit	38.69

Statistical analysis title	Statistical analysis 18
Statistical analysis description: SDAI: Remission: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.672
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.51
upper limit	11.51

Statistical analysis title	Statistical analysis 19
Statistical analysis description: SDAI: Remission: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.03
upper limit	8

Statistical analysis title	Statistical analysis 20
Statistical analysis description: SDAI: Remission: Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.07
upper limit	18.45

Statistical analysis title	Statistical analysis 21
Statistical analysis description: SDAI: Remission: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	17.25

Statistical analysis title	Statistical analysis 22
Statistical analysis description: SDAI: Remission: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	20.57

Secondary: Change of CDAI and SDAI at each visit during Period 1.

End point title	Change of CDAI and SDAI at each visit during Period 1.

End point description:

SDAI and CDAI are defined as: 1) SDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0-28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) + hs CRP (in mg/dL) in Period 1. 2) CDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0 28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) in Period 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
CDAI Week 4 (N= 473)	-16.78 (± 11.72)			
CDAI Week 8 (N= 473)	-21.69 (± 12.4)			
CDAI Week 16 (N= 473)	-25.77 (± 13.19)			
CDAI Week 24 (N= 473)	-29.25 (± 13.66)			
SDAI Week 4 (N= 465)	-18.19 (± 12.44)			
SDAI Week 8 (N= 471)	-23.06 (± 12.89)			
SDAI Week 16 (N= 472)	-27.17 (± 13.61)			
SDAI Week 24 (N= 472)	-30.56 (± 14.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of CDAI and SDAI at each visit during Period 2

End point title	Change of CDAI and SDAI at each visit during Period 2

End point description:

SDAI and CDAI are defined as: 1) SDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0-28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) + hs CRP (in mg/dL) in Period 2. 2) CDAI = DAS28 prorated Swollen Joint Count (0-28) + DAS28 prorated Tender Joint Count (0 28) + Physician Global Assessment of arthritis (0-10) + Subject Global Assessment of arthritis (0-10) in Period 2.

End point type	Secondary

End point timeframe:
Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
CDAI: Week 24 (N= 163, 168)	-32.11 (± 12.06)	-32.23 (± 12.49)		
CDAI: Week 28 (N= 163, 168)	-29.62 (± 13.1)	-26.49 (± 15.87)		
CDAI: Week 36 (N= 163, 168)	-28.71 (± 13.56)	-24.33 (± 16.45)		
CDAI: Week 44 (N= 163, 168)	-28.63 (± 13.58)	-23.81 (± 16.48)		
CDAI: Week 52 (N= 163, 168)	-28.3 (± 13.61)	-23.52 (± 15.98)		
SDAI: Week 24 (N= 163, 168)	-33.61 (± 12.07)	-33.68 (± 13.03)		
SDAI: Week 28 (N= 160, 166)	-31.07 (± 13.58)	-27.58 (± 16.5)		
SDAI: Week 36 (N= 162, 167)	-30.2 (± 14.05)	-25.44 (± 17.17)		
SDAI: Week 44 (N= 162, 167)	-30.21 (± 14.14)	-24.85 (± 17.29)		
SDAI: Week 52 (N= 162, 167)	-29.86 (± 14.03)	-24.57 (± 16.79)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: CDAI: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	-0.01

Statistical analysis title	Statistical analysis 2
Statistical analysis description: CDAI: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.72
upper limit	-1.05

Statistical analysis title	Statistical analysis 3
Statistical analysis description: CDAI: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.37
upper limit	-1.67

Statistical analysis title	Statistical analysis 4
Statistical analysis description: CDAI: Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.36
upper limit	-1.68

Statistical analysis title	Statistical analysis 5
Statistical analysis description: SDAI: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	-0.03

Statistical analysis title	Statistical analysis 6
Statistical analysis description: SDAI: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.97
upper limit	-1.12

Statistical analysis title	Statistical analysis 7
Statistical analysis description: SDAI: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.78
upper limit	-1.88

Statistical analysis title	Statistical analysis 8
Statistical analysis description: SDAI: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	-1.84

Secondary: Proportion of participants achieving American College of Rheumatology (ACR) ACR20, ACR50, ACR70 and ACR90 (by 66/68 joint counts) during Period 1 at each visit.

End point title	Proportion of participants achieving American College of Rheumatology (ACR) ACR20, ACR50, ACR70 and ACR90 (by 66/68 joint counts) during Period 1 at each visit.

End point description:

A 66 swollen and 68 tender joint count was used for calculating ACR responses. The ACR's definition for calculating improvement in RA (ACR20) was calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: subject and

physician global assessments of arthritis, pain, disability, and an acute phase reactant. Similarly, ACR50, ACR70 and ACR90 were calculated with the respective percent improvement. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: percentage of participants				
number (not applicable)				
ACR 20: Week 4 (N= 469)	58.6			
ACR 20: Week 8 (N= 469)	73.1			
ACR 20: Week 16 (N= 469)	83.6			
ACR 20: Week 24 (N= 469)	87.8			
ACR 50: Week 4 (N= 469)	19.8			
ACR 50: Week 8 (N= 469)	35.8			
ACR 50: Week 16 (N= 469)	55.2			
ACR 50: Week 24 (N= 469)	72.5			
ACR 70: Week 4 (N= 469)	4.3			
ACR 70: Week 8 (N= 469)	11.1			
ACR 70: Week 16 (N= 469)	23.7			
ACR 70: Week 24 (N= 469)	39.4			
ACR 90: Week 4 (N= 469)	0			
ACR 90: Week 8 (N= 469)	0.4			
ACR 90: Week 16 (N= 469)	1.5			
ACR 90: Week 24 (N= 469)	5.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants achieving ACR20, ACR50, ACR70 and ACR90 (by 66/68 joint counts) during Period 2 at each visit.

End point title	Proportion of participants achieving ACR20, ACR50, ACR70 and ACR90 (by 66/68 joint counts) during Period 2 at each visit.

End point description:

A 66 swollen and 68 tender joint count was used for calculating ACR responses. The ACR's definition for calculating improvement in RA (ACR20) was calculated as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core set measures: subject and physician global assessments of arthritis, pain, disability, and an acute phase reactant. Similarly, ACR50, ACR70 and ACR90 were calculated with the respective percent improvement. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: Percentage of participants				
number (not applicable)				
ACR 20: Week 24 (N= 161, 168)	96.3	96.4		
ACR 20: Week 28 (N= 161, 168)	91.3	81.5		
ACR 20: Week 36 (N= 161, 168)	88.2	76.8		
ACR 20: Week 44 (N= 161, 168)	86.3	76.2		
ACR 20: Week 52 (N= 161, 168)	87	76.2		
ACR 50: Week 24 (N= 161, 168)	88.2	85.7		
ACR 50: Week 28 (N= 161, 168)	75.2	63.7		
ACR 50: Week 36 (N= 161, 168)	68.9	51.8		
ACR 50: Week 44 (N= 161, 168)	69.6	50.6		
ACR 50: Week 52 (N= 161, 168)	68.3	50.6		
ACR 70: Week 24 (N= 161, 168)	49.7	52.4		
ACR 70: Week 28 (N= 161, 168)	41	33.9		
ACR 70: Week 36 (N= 161, 168)	44.7	27.4		
ACR 70: Week 44 (N= 161, 168)	43.5	25		
ACR 70: Week 52 (N= 161, 168)	41	25		
ACR 90: Week 24 (N= 161, 168)	8.1	8.3		
ACR 90: Week 28 (N= 161, 168)	8.7	5.4		
ACR 90: Week 36 (N= 161, 168)	11.8	5.4		
ACR 90: Week 44 (N= 161, 168)	9.3	4.8		
ACR 90: Week 52 (N= 161, 168)	13	7.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: ACR 20: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.21
upper limit	3.9

Statistical analysis title	Statistical analysis 2
Statistical analysis description: ACR 20: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.45
upper limit	17.06

Statistical analysis title	Statistical analysis 3
Statistical analysis description: ACR 20: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.31
upper limit	19.51

Statistical analysis title	Statistical analysis 4
Statistical analysis description: ACR 20: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	18.49

Statistical analysis title	Statistical analysis 5
Statistical analysis description: ACR 20: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	10.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	19.05

Statistical analysis title	Statistical analysis 6
Statistical analysis description: ACR 50: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.584
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.78
upper limit	9.75

Statistical analysis title	Statistical analysis 7
Statistical analysis description: ACR 50: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.59
upper limit	21.34

Statistical analysis title	Statistical analysis 8
Statistical analysis description: ACR 50: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.76
upper limit	27.56

Statistical analysis title	Statistical analysis 9
Statistical analysis description: ACR 50: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.59
upper limit	29.35

Statistical analysis title	Statistical analysis 10
Statistical analysis description: ACR 50: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	17.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.3
upper limit	28.16

Statistical analysis title	Statistical analysis 11
Statistical analysis description: ACR 70: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.702
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Proportions
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.49
upper limit	8.11

Statistical analysis title	Statistical analysis 12
Statistical analysis description: ACR 70: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.37
upper limit	17.5

Statistical analysis title	Statistical analysis 13
Statistical analysis description: ACR 70: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.12
upper limit	27.56

Statistical analysis title	Statistical analysis 14
Statistical analysis description: ACR 70: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.4
upper limit	28.55

Statistical analysis title	Statistical analysis 15
Statistical analysis description: ACR 70: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.96
upper limit	26.02

Statistical analysis title	Statistical analysis 16
Statistical analysis description: ACR 90: Week 24	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.921
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.19
upper limit	5.67

Statistical analysis title	Statistical analysis 17
Statistical analysis description: ACR 90: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.19
upper limit	8.86

Statistical analysis title	Statistical analysis 18
Statistical analysis description: ACR 90: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	12.48

Statistical analysis title	Statistical analysis 19
Statistical analysis description: ACR 90: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	10.08

Statistical analysis title	Statistical analysis 20
Statistical analysis description:	
ACR 90: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.196
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in proportions
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	12.4

Secondary: Change in the tender and swollen joint counts at each visit during Period 1 (using 28 joint count as well as 66/68 joint counts).

End point title	Change in the tender and swollen joint counts at each visit during Period 1 (using 28 joint count as well as 66/68 joint counts).

End point description:

A total of 66 swollen and 68 tender joints were assessed for tenderness/pain and swelling by the same qualified personnel (when possible) at each visit. For ACR responses, a 66/68 joint count was used. For DAS28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) calculations, the 28 joint count was used, which included: shoulders, elbows, wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: Percentage of participants				
arithmetic mean (standard deviation)				
28 Tender Joint Count: Week 4	-6.49 (± 6.07)			
28 Tender Joint Count: Week 8	-8.59 (± 6.32)			
28 Tender Joint Count: Week 16	-10.12 (± 6.82)			
28 Tender Joint Count: Week 24	-11.5 (± 6.79)			
28 Swollen Joint Count: Week 4	-5.52 (± 5.02)			
28 Swollen Joint Count: Week 8	-7.04 (± 5.36)			
28 Swollen Joint Count: Week 16	-8.21 (± 5.44)			
28 Swollen Joint Count: Week 24	-9.01 (± 5.65)			
68 Tender Joint Count: Week 4	-9.71 (± 10)			
68 Tender Joint Count: Week 8	-13.02 (± 10.95)			
68 Tender Joint Count: Week 16	-15.21 (± 11.9)			
68 Tender Joint Count: Week 24	-17.41 (± 12.72)			
68 Swollen Joint Count: Week 4	-7.12 (± 6.86)			
68 Swollen Joint Count: Week 8	-9.03 (± 7.54)			
68 Swollen Joint Count: Week 16	-10.49 (± 7.62)			
68 Swollen Joint Count: Week 24	-11.53 (± 8.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the tender and swollen joint counts at each visit during Period 2 (using 28 joint count as well as 66/68 joint counts).

End point title	Change in the tender and swollen joint counts at each visit during Period 2 (using 28 joint count as well as 66/68 joint counts).

End point description:

A total of 66 swollen and 68 tender joints were assessed for tenderness/pain and swelling by the same qualified personnel (when possible) at each visit. For ACR responses, a 66/68 joint count was used. For DAS28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) calculations, the 28 joint count was used, which included: shoulders, elbows, wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
28 Tender Joint Count: Week 24	-12.65 (± 6.25)	-12.35 (± 6.45)		
28 Tender Joint Count: Week 28	-11.69 (± 6.74)	-10.08 (± 7.84)		
28 Tender Joint Count: Week 36	-11.22 (± 6.91)	-9.23 (± 8.07)		
28 Tender Joint Count: Week 44	-11.19 (± 6.82)	-8.97 (± 8.01)		
28 Tender Joint Count: Week 52	-11.03 (± 6.81)	-8.78 (± 7.83)		
28 Swollen Joint Count: Week 24	-9.78 (± 5.16)	-9.98 (± 5.58)		
28 Swollen Joint Count: Week 28	-8.97 (± 5.27)	-8.7 (± 5.94)		
28 Swollen Joint Count: Week 36	-8.64 (± 5.51)	-8.16 (± 6.04)		
28 Swollen Joint Count: Week 44	-8.71 (± 5.52)	-8.03 (± 6.08)		
28 Swollen Joint Count: Week 52	-8.59 (± 5.42)	-7.98 (± 6.05)		
68 Tender Joint Count: Week 24	-18.31 (± 12.13)	-18.19 (± 12.03)		
68 Tender Joint Count: Week 28	-17.02 (± 12.48)	-15.2 (± 13.95)		
68 Tender Joint Count: Week 36	-17.27 (± 12.55)	-17.13 (± 14.28)		
68 Tender Joint Count: Week 44	-18.67 (± 12.9)	-18.82 (± 14.71)		
68 Tender Joint Count: Week 52	-17.88 (± 13.21)	-17.61 (± 12.57)		
68 Swollen Joint Count: Week 24	-12.09 (± 7.76)	-12.4 (± 8.45)		
68 Swollen Joint Count: Week 28	-11.23 (± 7.77)	-10.81 (± 8.66)		
68 Swollen Joint Count: Week 36	-11.26 (± 8.05)	-10.67 (± 8.59)		
68 Swollen Joint Count: Week 44	-12 (± 8.03)	-11.63 (± 8.58)		
68 Swollen Joint Count: Week 52	-11.98 (± 8.17)	-11.89 (± 8.91)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: 28 Tender Joint Count: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.84
upper limit	0.05

Statistical analysis title	Statistical analysis 2
Statistical analysis description: 28 Tender Joint Count: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	-0.27

Statistical analysis title	Statistical analysis 3
Statistical analysis description: 28 Tender Joint Count: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	-0.57

Statistical analysis title	Statistical analysis 4
Statistical analysis description: 28 Tender Joint Count: Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	-0.66

Statistical analysis title	Statistical analysis 5
Statistical analysis description: 28 Swollen Joint Count: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.5

Statistical analysis title	Statistical analysis 6
Statistical analysis description: 28 Swollen Joint Count: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.45

Statistical analysis title	Statistical analysis 7
Statistical analysis description: 28 Swollen Joint Count: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	0.17

Statistical analysis title	Statistical analysis 8
Statistical analysis description: 28 Swollen Joint Count: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.25

Statistical analysis title	Statistical analysis 9
Statistical analysis description: 68 Tender Joint Count: Week 28	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.28

Statistical analysis title	Statistical analysis 10
Statistical analysis description: 68 Tender Joint Count: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.42
upper limit	-0.35

Statistical analysis title	Statistical analysis 11
Statistical analysis description: 68 Tender Joint Count: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.91
upper limit	-0.76

Statistical analysis title	Statistical analysis 12
Statistical analysis description: 68 Tender Joint Count: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	-0.97

Statistical analysis title	Statistical analysis 13
Statistical analysis description: 68 Swollen Joint Count: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	0.42

Statistical analysis title	Statistical analysis 14
Statistical analysis description: 68 Swollen Joint Count: Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	0.32

Statistical analysis title	Statistical analysis 15
Statistical analysis description: 68 Swollen Joint Count: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	0.05

Statistical analysis title	Statistical analysis 16
Statistical analysis description: 68 Swollen Joint Count: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	0.1

Secondary: Change in the Physician Global Assessment of arthritis at each visit during Period 1

End point title	Change in the Physician Global Assessment of arthritis at each visit during Period 1

End point description:

The investigator estimated the subject's overall disease activity over the last 2 to 3 days (independent of the Subject Global Assessment of arthritis) using a scale between 0 (no disease activity) and 10 (extreme disease activity) and marking one number with an 'X'.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 473)	-2.6 (± 1.78)			
Week 8 (N= 473)	-3.46 (± 1.9)			
Week 16 (N= 473)	-4.12 (± 1.96)			
Week 24 (N= 473)	-4.79 (± 2.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Physician Global Assessment of arthritis at each visit during Period 2

End point title	Change in the Physician Global Assessment of arthritis at each visit during Period 2

End point description:

The investigator estimated the subject's overall disease activity over the last 2 to 3 days (independent of the Subject Global Assessment of arthritis) using a scale between 0 (no disease activity) and 10 (extreme disease activity) and marking one number with an 'X'.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24	-5.28 (± 1.56)	-5.26 (± 1.78)		
Week 28	-4.93 (± 1.78)	-4.23 (± 2.43)		
Week 36	-4.83 (± 1.86)	-3.89 (± 2.48)		
Week 44	-4.82 (± 2.02)	-3.79 (± 2.53)		
Week 52	-4.77 (± 2.03)	-3.74 (± 2.43)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.16

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.38

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	-0.54

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.53

Secondary: Change in the Subject Global Assessment of arthritis in Period 1

End point title	Change in the Subject Global Assessment of arthritis in Period 1

End point description:

Subjects assessed their overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity), which corresponded to the magnitude of their pain) and marked one number with an 'X'.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 473)	-2.18 (± 2.21)			
Week 8 (N= 473)	-2.6 (± 2.34)			
Week 16 (N= 473)	-3.32 (± 2.44)			
Week 24 (N= 473)	-3.97 (± 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Subject Global Assessment of arthritis in Period 2

End point title	Change in the Subject Global Assessment of arthritis in Period 2

End point description:

Subjects assessed their overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity), which corresponded to the magnitude of their pain) and marked one number with an 'X'.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24	-4.39 (± 2.43)	-4.64 (± 2.16)		
Week 28	-4.03 (± 2.7)	-3.48 (± 2.94)		
Week 36	-4.02 (± 2.71)	-3.05 (± 2.94)		
Week 44	-3.92 (± 2.79)	-3.02 (± 2.91)		
Week 52	-3.91 (± 2.84)	-3.02 (± 2.91)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.01

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	-0.43

Statistical analysis title	Statistical analysis 3
Statistical analysis description: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.33

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.31

Secondary: Change in morning stiffness (measured in minutes) at each visit during Period 1

End point title	Change in morning stiffness (measured in minutes) at each visit during Period 1
End point description:	
Morning stiffness was defined as stiffness in and around the joints, lasting at least 1 hour before maximal improvement. Participants assessed their overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity), which corresponded to the magnitude of their pain) and marked one number with an 'X'.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 4, 8, 16 and 24	

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: minutes				
arithmetic mean (standard deviation)				
Week 4 (N= 467)	-78.56 (± 143.68)			
Week 8 (N= 467)	-90.58 (± 147.42)			

Week 16 (N= 467)	-102.25 (± 158.76)			
Week 24 (N= 467)	-109.32 (± 183.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in morning stiffness (measured in minutes) at each visit during Period 2

End point title	Change in morning stiffness (measured in minutes) at each visit during Period 2

End point description:

Morning stiffness was defined as stiffness in and around the joints, lasting at least 1 hour before maximal improvement. Participants assessed their overall disease activity over the last 2 to 3 days using a scale between 0 (no disease activity) and 10 (extreme disease activity), which corresponded to the magnitude of their pain) and marked one number with an 'X'.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 24 (N= 163, 166)	-118.3 (± 171.15)	-121.93 (± 186.17)		
Week 28 (N= 163, 166)	-134.42 (± 224.7)	-109.57 (± 163.79)		
Week 36 (N= 163, 166)	-132.05 (± 224.86)	-104.4 (± 164.13)		
Week 44 (N= 163, 166)	-129.86 (± 223.78)	-103.14 (± 162.65)		
Week 52 (N= 163, 166)	-129.49 (± 223.68)	-100.31 (± 153.62)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Week 28

Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.07
upper limit	-1.16

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-17.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.39
upper limit	-3.68

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-16.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.35
upper limit	-2.73

Statistical analysis title	Statistical analysis 4
Statistical analysis description: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-19.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.78
upper limit	-5.54

Secondary: Change in the Subject General Health Visual Analog Scale (VAS) and Pain VAS at each visit during Period 1

End point title	Change in the Subject General Health Visual Analog Scale (VAS) and Pain VAS at each visit during Period 1

End point description:

Participants were asked to answer the question "In general how would you rate your health over the last 2 3 weeks?" by marking a vertical line at the appropriate position through the 100 mm VAS. The length on the line was measured from the left (in mm). For Pain VAS, participants assessed the severity of their arthritis pain during the last 2 to 3 days using a 100 mm VAS by marking a vertical line at the appropriate position on the scale between 0 (no pain) and 100 (most severe pain), which corresponded to the magnitude of their pain.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
General Health VAS: Week 4 (N= 473)	-20.2 (± 22.22)			
General Health VAS: Week 8 (N= 473)	-25.17 (± 24.59)			
General Health VAS: Week 16 (N= 473)	-32.54 (± 24.89)			
General Health VAS: Week 24 (N= 473)	-40.67 (± 26.28)			

Pain VAS: Week 4 (N= 473)	-24.07 (± 22.56)			
Pain VAS: Week 8 (N= 473)	-28.55 (± 24.08)			
Pain VAS: Week 16 (N= 473)	-35.2 (± 24.81)			
Pain VAS: Week 24 (N= 473)	-42.49 (± 26.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Subject General Health VAS and Pain VAS at each visit during Period 2

End point title	Change in the Subject General Health VAS and Pain VAS at each visit during Period 2

End point description:

Participants were asked to answer the question "In general how would you rate your health over the last 2 3 weeks?" by marking a vertical line at the appropriate position through the 100 mm VAS. The length on the line was measured from the left (in mm). For Pain VAS, participants assessed the severity of their arthritis pain during the last 2 to 3 days using a 100 mm VAS by marking a vertical line at the appropriate position on the scale between 0 (no pain) and 100 (most severe pain), which corresponded to the magnitude of their pain.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
General Health VAS: Week 24	-46.66 (± 24.72)	-47.53 (± 20.21)		
General Health VAS: Week 28	-41.31 (± 27.01)	-34.95 (± 28.95)		
General Health VAS: Week 36	-39.84 (± 26.56)	-30.74 (± 29.79)		
General Health VAS: Week 44	-39.82 (± 27.61)	-30.1 (± 29.88)		
General Health VAS: Week 52	-39.81 (± 28.16)	-29.67 (± 29.21)		
Pain VAS: Week 24	-46.61 (± 24.33)	-49.69 (± 20.64)		
Pain VAS: Week 28	-43.3 (± 36.34)	-38.17 (± 29.24)		
Pain VAS: Week 36	-41.42 (± 27.01)	-34 (± 30.3)		
Pain VAS: Week 44	-41.21 (± 28.01)	-33.07 (± 29.46)		

Pain VAS: Week 52	-40.95 (± 28.61)	-32.91 (± 29.26)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: General Health VAS: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.91
upper limit	0.48

Statistical analysis title	Statistical analysis 2
Statistical analysis description: General Health VAS: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.49
upper limit	-2.59

Statistical analysis title	Statistical analysis 3
Statistical analysis description: General Health VAS: Week 44	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.2
upper limit	-3.18

Statistical analysis title	Statistical analysis 4
Statistical analysis description: General Health VAS: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.64
upper limit	-3.55

Statistical analysis title	Statistical analysis 5
Statistical analysis description: Pain VAS: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.75
upper limit	-1.06

Statistical analysis title	Statistical analysis 6
Statistical analysis description: Pain VAS: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.85
upper limit	-3.34

Statistical analysis title	Statistical analysis 7
Statistical analysis description: Pain VAS: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.72
upper limit	-4.26

Statistical analysis title	Statistical analysis 8
Statistical analysis description: Pain VAS: Week 52	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.6
upper limit	-3.99

Secondary: Change in CRP and ESR at each visit during Period 1

End point title	Change in CRP and ESR at each visit during Period 1

End point description:

The DAS assessment is a derived measurement with differential weight given to each component. The DAS28-ESR and DAS28-CRP was calculated at every visit within the clinical database in period 1. The components of the DAS28 ESR score assessment are: Tender/ Painful Joint Count (28), Swollen Joint Count (28); ESR, Subject General Health VAS assessment. The components of the DAS28 CRP score assessment were: Tender/Painful Joint Count (28); Swollen Joint Count (28), hsCRP, and the Subject General Health VAS assessment. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16 and 24

End point values	Open-Label Treatment			
Subject group type	Reporting group			
Number of subjects analysed	478			
Units: units on a scale				
arithmetic mean (standard deviation)				
CRP: Week 4 (N= 465)	-14.07 (± 25.3)			
CRP: Week 8 (N= 471)	-14.43 (± 23.51)			
CRP: Week 16 (N= 472)	-14.71 (± 27.32)			
CRP: Week 24 (N= 472)	-14.51 (± 27.64)			
ESR: Week 4 (N= 473)	-17.32 (± 19.44)			
ESR: Week 8 (N= 473)	-19.28 (± 21.62)			
ESR: Week 16 (N= 473)	-21.1 (± 24.2)			
ESR: Week 24 (N= 473)	-26.77 (± 26.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CRP and ESR at each visit during Period 2

End point title	Change in CRP and ESR at each visit during Period 2

End point description:

The DAS assessment is a derived measurement with differential weight given to each component. The DAS28-ESR and DAS28-CRP was calculated at every visit within the clinical database in period 1. The components of the DAS28 ESR score assessment are: Tender/ Painful Joint Count (28), Swollen Joint Count (28); ESR, Subject General Health VAS assessment. The components of the DAS28 CRP score assessment were: Tender/Painful Joint Count (28); Swollen Joint Count (28), hsCRP, and the Subject General Health VAS assessment. This efficacy measurement was made at every study visit.

End point type	Secondary

End point timeframe:

Baseline, Weeks 24, 28, 36, 44 and 52

End point values	Etanercept	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	168		
Units: units on a scale				
arithmetic mean (standard deviation)				
CRP: Week 24 (N= 161, 168)	-16.92 (± 28.64)	-14.47 (± 21.59)		
CRP: Week 28 (N= 160, 166)	-15.94 (± 28.52)	-8.89 (± 25.46)		
CRP: Week 36 (N= 162, 167)	-15.56 (± 31.36)	-7.45 (± 25.55)		
CRP: Week 44 (N= 162, 167)	-16.47 (± 30.09)	-6.72 (± 26.32)		
CRP: Week 52 (N= 162, 167)	-16.29 (± 30.74)	-7.07 (± 26.76)		
ESR: Week 24 (N= 163, 168)	-31.52 (± 22.55)	-31.02 (± 24.24)		
ESR: Week 28 (N= 163, 168)	-26.96 (± 23.04)	-20.28 (± 23.68)		
ESR: Week 36 (N= 163, 168)	-26.1 (± 24.17)	-16.94 (± 23.08)		
ESR: Week 44 (N= 163, 168)	-24.39 (± 22.99)	-16.14 (± 23.1)		
ESR: Week 52 (N= 163, 168)	-23.56 (± 21.88)	-16.27 (± 22.65)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

CRP: Week 28

Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.39
upper limit	-1.05

Statistical analysis title	Statistical analysis 2
Statistical analysis description: CRP: Week 36	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.09
upper limit	-1.46

Statistical analysis title	Statistical analysis 3
Statistical analysis description: CRP: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.06
upper limit	-3.44

Statistical analysis title	Statistical analysis 4
Statistical analysis description: CRP: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.48
upper limit	-2.85

Statistical analysis title	Statistical analysis 5
Statistical analysis description: ESR: Week 28	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.23
upper limit	-2.49

Statistical analysis title	Statistical analysis 6
Statistical analysis description: ESR: Week 36	
Comparison groups	Etanercept v Placebo

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.33
upper limit	-5.05

Statistical analysis title	Statistical analysis 7
Statistical analysis description: ESR: Week 44	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.38
upper limit	-3.8

Statistical analysis title	Statistical analysis 8
Statistical analysis description: ESR: Week 52	
Comparison groups	Etanercept v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.03
upper limit	-2.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of the informed consent to 28 days after the last dose of study medication through the last participant's visit.

Adverse event reporting additional description:

The Open Label Safety Population is defined as all participants who had at least one dose of open label study drug during Period 1. The Double Blind Safety Population is defined as all randomized participants who had at least one dose of study drug during period 2.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Open-Label Treatment

Reporting group description:

Participants in open-label treatment received ETN 50 mg with MTX (with or without other DMARDs).

Reporting group title	Etanercept

Reporting group description:

Participants were randomized to receive ETN 50 mg QW with MTX (with or without other DMARDs).

Reporting group title	Placebo

Reporting group description:

Participants were randomized to receive PBO 50 mg QW + MTX (with or without DMARDs).

Serious adverse events	Open-Label Treatment	Etanercept	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 489 (2.66%)	0 / 167 (0.00%)	7 / 176 (3.98%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			

subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			

subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 489 (0.00%)	0 / 167 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural abscess			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			

subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella sepsis			
subjects affected / exposed	1 / 489 (0.20%)	0 / 167 (0.00%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Open-Label Treatment	Etanercept	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 489 (5.32%)	4 / 167 (2.40%)	9 / 176 (5.11%)
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	26 / 489 (5.32%)	4 / 167 (2.40%)	9 / 176 (5.11%)
occurrences (all)	28	4	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2012	In the protocol amendment 1, Clarifications to the details of MTX treatment, MTX supply, and medication errors. Changes to planned analyses: Site 1033 in the crimea was terminated early due to the Russian-Ukraine conflict. Participant exclusion from the analysis population was described in Section 10.2.
22 March 2013	In the protocol amendment 2, Clarifications to the Schedule of Activities; QFT testing language; number of sites and countries; definitions of loss of LDA and achieving LDA DAS28 ESR scores; Arm B dosing frequency; language to allow for possible re screenings; contact for breaking the blind; MTX supplies; language for MTX formulation and packaging; personnel performing 66/68 joint assessment; witness consent; reportable information; pregnancy testing language and exposure during pregnancy; laboratory determinations (TB testing was to be handled by a centralized laboratory and hs CRP testing to be done); AE reporting and other reportable information; and publication of study results. Clarifications to inclusion and exclusion criteria. Added a section on the sponsor's qualified medical personnel and a section on protocol specified SAEs; added occupational exposure to definition of AEs; updated the version of the OMERACT flare questionnaire; added language that MTX was to be considered an IP; added the storage condition of MTX; added language to clarify when liver function tests were not required as a routine procedure; and added language on latex in Appendix 9 of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported