Clinical trial results:
A Randomized Withdrawal Double-blind Study of Etanercept Monotherapy Compared to Methotrexate Monotherapy for Maintenance of Remission in Subjects With Rheumatoid Arthritis

Summary

EudraCT number	2014-004868-38
Trial protocol	GR CZ HU PT BG ES FR DE IT
Global end of trial date	06 December 2019

Results information

Result version number	v1 (current)
This version publication date	10 December 2020
First version publication date	10 December 2020

Trial information

Trial identification

Sponsor protocol code	20110186

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02373813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	06 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of etanercept monotherapy compared to methotrexate monotherapy on maintenance of remission in subjects with rheumatoid arthritis (RA) who were on etanercept plus methotrexate combination therapy.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Before a subject's participation in the clinical study, the investigator was responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) were administered.

Background therapy:

Participants also receive folic acid 5 to 7 mg per week as per investigator judgment or according to local standard of care.

Evidence for comparator: -

Actual start date of recruitment	20 February 2015
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	Argentina: 2
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 35
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United States: 181

Worldwide total number of subjects	371
EEA total number of subjects	135

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)	266
From 65 to 84 years	104
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 97 centers in Canada, United States, Argentina, Bulgaria, Czech Republic, Spain, France, Germany, Greece, Hungary, Italy, Mexico, Poland, Portugal, and South Africa. The first participant enrolled on 20 February 2015; the last participant enrolled on 26 June 2018.

Pre-assignment

Screening details:

After a 24-week open label run-in period, participants were randomly assigned in a 2:2:1 ratio to one of three treatment groups: methotrexate monotherapy, etanercept monotherapy, or etanercept plus methotrexate.

Period 1

Period 1 title	Run-In Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label Run-In: Etanercept plus Methotrexate

Arm description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 24 weeks. Participants also receive folic acid as standard of care.

Arm type	Experimental
Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	Enbrel
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etanercept dosing in the study followed the recommended label dosing for subjects with RA (subcutaneous injection, 50 mg once weekly).

Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate dosing in the study will be 10 to 25 mg weekly, consistent with the participant’s dosing prior to screening.

Number of subjects in period 1	Open Label Run-In: Etanercept plus Methotrexate
Started	371
Treated	368
Completed	254
Not completed	117
Consent withdrawn by subject	16

No Case Report Form	1
Ineligibility Determined	3
Adverse event, non-fatal	3
Decision by Sponsor	11
Lost to follow-up	2
Other, Not Specified	5
Protocol deviation	75
Noncompliance	1

Period 2

Period 2 title	Double-Blind Treatment Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a double-blind study; both participants and investigators were blinded to treatment assignments. A participant's treatment assignment was only to be unblinded when knowledge of the treatment was essential for the further management of the participant on this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Treatment: Methotrexate Monotherapy

Arm description:

Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.

Arm type	Experimental
Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	Enbrel
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etanercept dosing in the study followed the recommended label dosing for subjects with RA (subcutaneous injection, 50 mg once weekly). Used as rescue treatment in this arm as needed.

Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate dosing in the study will be 10 to 25 mg weekly, consistent with the participant’s dosing prior to screening.

Investigational medicinal product name	Placebo for etanercept
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

During the double-blind treatment period, participants receive 1 dose of etanercept placebo per week (scheduled approximately 7 days apart) for 48 weeks.

Arm title	Double-Blind Treatment: Etanercept Monotherapy

Arm description:

Etanercept 50 mg weekly by subcutaneous injection plus placebo for methotrexate for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.

Arm type	Experimental
Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	Enbrel
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etanercept dosing in the study followed the recommended label dosing for subjects with RA (subcutaneous injection, 50 mg once weekly).

Investigational medicinal product name	Placebo for methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During the double-blind treatment period, methotrexate placebo capsules were taken once weekly by oral administration.

Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate dosing in the study will be 10 to 25 mg weekly, consistent with the participant’s dosing prior to screening. Used as rescue treatment in this arm as needed.

Arm title	Double-Blind Treatment: Etanercept plus Methotrexate

Arm description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening continued on the assigned treatments (as rescue treatment). Participants also receive folic acid as standard of care.

Arm type	Experimental
Investigational medicinal product name	methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate dosing in the study will be 10 to 25 mg weekly, consistent with the participant’s dosing prior to screening.

Investigational medicinal product name	etanercept
Investigational medicinal product code	
Other name	Enbrel

Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Etanercept dosing in the study followed the recommended label dosing for subjects with RA (subcutaneous injection, 50 mg once weekly).

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was a run-in period.

Number of subjects in period 2[2][3]	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate
Started	101	101	51
Received Investigational Product (IP)	101	100	51
Received Rescue Treatment	52 [4]	36 [5]	15 [6]
Completed	88	92	47
Not completed	13	9	4
Consent withdrawn by subject	10	6	3
Decision by Sponsor	1	2	-
Lost to follow-up	-	1	1
Protocol deviation	2	-	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The double-blind treatment period was preceded by a run-in period.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One participant who completed the run-in period was not randomized.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who received rescue treatment in each arm.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who received rescue treatment in each arm.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who received rescue treatment in each arm.

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Treatment: Methotrexate Monotherapy
Reporting group description:	
Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.	
Reporting group title	Double-Blind Treatment: Etanercept Monotherapy
Reporting group description:	
Etanercept 50 mg weekly by subcutaneous injection plus placebo for methotrexate for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.	
Reporting group title	Double-Blind Treatment: Etanercept plus Methotrexate
Reporting group description:	
Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening continued on the assigned treatments (as rescue treatment). Participants also receive folic acid as standard of care.	

Reporting group values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects	101	101	51
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.2	54.8	55.9
standard deviation	± 11.4	± 12.8	± 12.6
Sex: Female, Male Units:			
Female	76	77	40
Male	25	24	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13	19	8
Not Hispanic or Latino	88	82	43
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	4	3	2
Asian	2	0	1
Black	3	7	5
White	92	86	42
Other, Not Specified	0	5	1

Reporting group values	Total		
Number of subjects	253		

Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units:			
Female	193		
Male	60		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	40		
Not Hispanic or Latino	213		
Unknown or Not Reported	0		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	9		
Asian	3		
Black	15		
White	220		
Other, Not Specified	6		

End points

End points reporting groups

Reporting group title	Open Label Run-In: Etanercept plus Methotrexate

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 24 weeks. Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Methotrexate Monotherapy

Reporting group description:

Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Etanercept Monotherapy

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus placebo for methotrexate for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg). Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Etanercept plus Methotrexate

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 48 weeks. After randomization, a participant experiencing protocol-defined disease worsening continued on the assigned treatments (as rescue treatment). Participants also receive folic acid as standard of care.

Primary: Percentage of Participants with Simplified Disease Activity Index (SDAI) Remission (≤ 3.3) at Week 48: Etanercept Monotherapy vs. Methotrexate Monotherapy

End point title	Percentage of Participants with Simplified Disease Activity Index (SDAI) Remission (≤ 3.3) at Week 48: Etanercept Monotherapy vs. Methotrexate Monotherapy[1]

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Primary Analysis Set: all randomized participants. Nonresponder imputation.

End point type	Primary

End point timeframe:

Week 48

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint was to compare only these 2 arms: Etanercept Monotherapy vs. Methotrexate Monotherapy.

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	101		
Units: percentage of participants				

number (not applicable)	28.7	49.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [2]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	33.9
Variability estimate	Standard error of the mean
Dispersion value	6.7

Notes:

[2] - The risk difference and its p-value were estimated from the chi-squared test with continuity correction.

Secondary: Percentage of Participants with SDAI Remission (≤ 3.3) at Week 48: Etanercept and Methotrexate vs. Methotrexate Monotherapy

End point title	Percentage of Participants with SDAI Remission (≤ 3.3) at Week 48: Etanercept and Methotrexate vs. Methotrexate Monotherapy[3]

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Primary Analysis Set: all randomized participants. Nonresponder imputation.

End point type	Secondary

End point timeframe:

Week 48

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary endpoint was to compare only these 2 arms: Etanercept Monotherapy vs. Methotrexate Monotherapy.

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	51		
Units: percentage of participants				
number (not applicable)	28.7	52.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [4]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.9
upper limit	40.5
Variability estimate	Standard error of the mean
Dispersion value	8.3

Notes:

[4] - The risk difference and its p-value were estimated from the chi-squared test with continuity correction.

Secondary: SDAI Score at All Measured Timepoints

End point title	SDAI Score at All Measured Timepoints

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease.

Primary Analysis Set: all randomized participants. Observed cases at given timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[5]	101[6]	51[7]	
Units: score on a scale				
arithmetic mean (standard error)				
Baseline; n=100, 101, 51	1.29 (± 0.10)	1.2 (± 0.14)	1.18 (± 0.17)	
Week 12; n=100, 100, 51	7.01 (± 1.01)	4.37 (± 0.75)	4.39 (± 1.22)	
Week 24; n=92, 96, 49	5.61 (± 0.98)	4.98 (± 0.92)	3.28 (± 0.77)	
Week 36; n=89, 93, 48	4.03 (± 0.62)	2.25 (± 0.36)	2.41 (± 0.40)	
Week 48; n=84, 90, 47	3.41 (± 0.40)	2.33 (± 0.23)	2.86 (± 0.92)	

Notes:

[5] - n=observed cases at given timepoints

[6] - n=observed cases at given timepoints

[7] - n=observed cases at given timepoints

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Etanercept Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.31
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.89
upper limit	0.67
Variability estimate	Standard error of the mean
Dispersion value	1.66

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	1.26

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	1.46

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	2.01
Variability estimate	Standard error of the mean
Dispersion value	1.34

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.9

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.35
Variability estimate	Standard error of the mean
Dispersion value	0.71

Statistical analysis title	Statistical Analysis 9
Statistical analysis description: Week 48	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.55
upper limit	1.45
Variability estimate	Standard error of the mean
Dispersion value	0.87

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 48

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.99
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Change From Baseline in SDAI Score at All Measured Timepoints

End point title	Change From Baseline in SDAI Score at All Measured Timepoints

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3. A negative change from baseline indicates improvement.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[8]	101[9]	51[10]	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 12; n=99, 100, 51	5.67 (± 1.00)	3.14 (± 0.75)	3.21 (± 1.19)	
Change at Week 24; n=91, 96, 49	4.42 (± 0.98)	3.78 (± 0.91)	2.14 (± 0.78)	
Change at Week 36; n=88, 93, 48	2.90 (± 0.63)	1.06 (± 0.38)	1.30 (± 0.43)	
Change at Week 48; n=83, 90, 47	2.27 (± 0.39)	1.16 (± 0.24)	1.77 (± 0.94)	

Notes:

[8] - n=observed cases at given timepoint

[9] - n=observed cases at given timepoint

[10] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change at Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	0.77
Variability estimate	Standard error of the mean
Dispersion value	1.63

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change at Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-

	Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	1.25

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.75
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	1.45

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	1.34

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-0.39
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Change at Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	1.53
Variability estimate	Standard error of the mean
Dispersion value	0.88

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Change at Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Disease Activity Score (28 Joint) Calculated Using the Erythrocyte Sedimentation Rate Formula (DAS28-ESR) at All Measured Timepoints

End point title	Disease Activity Score (28 Joint) Calculated Using the Erythrocyte Sedimentation Rate Formula (DAS28-ESR) at All Measured Timepoints

End point description:

The DAS28-ESR is a modified composite index that was designed to measure disease activity using the number of tender and swollen joints based upon a 28-joint count, ESR in mm/hr, and a 100 mm VAS measuring the participant's general health, from 0 (best) to 100 (worst). DAS28-ESR scores range from 0 to 9.4, where higher scores represent higher disease activity.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[11]	101[12]	51[13]	
Units: score on a scale				
arithmetic mean (standard error)				
Baseline; n=100, 100, 51	1.80 (± 0.06)	1.88 (± 0.07)	1.84 (± 0.09)	
Week 12; n=99, 100, 51	2.78 (± 0.14)	2.37 (± 0.12)	2.32 (± 0.16)	
Week 24; n=92, 95, 49	2.41 (± 0.13)	2.54 (± 0.14)	2.17 (± 0.12)	
Week 36; n=87, 93, 48	2.32 (± 0.11)	2.17 (± 0.08)	2.16 (± 0.12)	
Week 48; n=85, 90, 47	2.22 (± 0.10)	2.21 (± 0.08)	2.11 (± 0.13)	

Notes:

[11] - n=observed cases at given timepoint

[12] - n=observed cases at given timepoint

[13] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Baseline

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.23

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Week 24	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.51
Variability estimate	Standard error of the mean
Dispersion value	0.19

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.13

Secondary: Change From Baseline in DAS28-ESR at All Measured Timepoints

End point title	Change From Baseline in DAS28-ESR at All Measured Timepoints

End point description:

The DAS28-ESR is a modified composite index that was designed to measure disease activity using the number of tender and swollen joints based upon a 28-joint count, ESR in mm/hr, and a 100 mm VAS measuring the participant's general health, from 0 (best) to 100 (worst). DAS28-ESR scores range from 0 to 9.4, where higher scores represent higher disease activity. A negative change from baseline indicates improvement.

Primary Analysis Set: all randomized participants. Observed cases at given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[14]	101[15]	51[16]	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 12; n=98, 100, 51	0.96 (± 0.13)	0.50 (± 0.10)	0.48 (± 0.18)	
Change at Week 24; n=91, 95, 49	0.65 (± 0.12)	0.69 (± 0.13)	0.34 (± 0.11)	
Change at Week 36; n=86, 92, 48	0.53 (± 0.10)	0.31 (± 0.08)	0.35 (± 0.12)	
Change at Week 48; n=84, 89, 47	0.43 (± 0.09)	0.34 (± 0.07)	0.32 (± 0.14)	

Notes:

[14] - n=observed cases at given time point

[15] - n=observed cases at given time point

[16] - n=observed cases at given time point

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change at Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.22

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change at Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.78
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.18

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.38
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Change at Week 48	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.11

Secondary: Disease Activity Score (28 Joint) Using the C-Reactive Protein Formula (DAS28-CRP) at All Measured Timepoints

End point title	Disease Activity Score (28 Joint) Using the C-Reactive Protein Formula (DAS28-CRP) at All Measured Timepoints

End point description:

The DAS28-CRP is a composite index that was designed to measure disease activity using the number of tender and swollen joints based upon a 28-joint count, CRP in mg/L, and a 100 mm VAS measuring the participant's general health from 0 (best) to 100 (worst). DAS28-CRP scores range from 0 to 9.4, where higher scores represent higher disease activity.

Primary Analysis Set: all randomized participants. Observed cases at given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[17]	101[18]	51[19]	
Units: score on a scale				
arithmetic mean (standard error)				
Baseline; n=101, 100, 51	1.50 (± 0.03)	1.50 (± 0.04)	1.54 (± 0.05)	
Week 12; n=100, 100, 51	2.36 (± 0.13)	1.91 (± 0.09)	1.94 (± 0.15)	
Week 24; n=92, 96, 49	2.15 (± 0.11)	2.00 (± 0.11)	1.77 (± 0.09)	
Week 36; n=89, 93, 48	1.96 (± 0.09)	1.67 (± 0.06)	1.72 (± 0.08)	
Week 48; n=84, 90, 47	1.87 (± 0.07)	1.67 (± 0.05)	1.72 (± 0.11)	

Notes:

[17] - n=observed cases at given time point

[18] - n=observed cases at given time point

[19] - n=observed cases at given time point

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.05

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 24	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Change From Baseline in DAS28-CRP at All Measured Timepoints

End point title	Change From Baseline in DAS28-CRP at All Measured Timepoints

End point description:

The DAS28-CRP is a composite index that was designed to measure disease activity using the number of tender and swollen joints based upon a 28-joint count, CRP in mg/L, and a 100 mm VAS measuring the participant's general health from 0 (best) to 100 (worst). DAS28-CRP scores range from 0 to 9.4, where higher scores represent higher disease activity. A negative change from baseline indicates improvement.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[20]	101[21]	51[22]	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 12; n=99,100, 51	0.84 (± 0.12)	0.42 (± 0.09)	0.41 (± 0.15)	
Change at Week 24; n=91, 96, 49	0.67 (± 0.11)	0.52 (± 0.11)	0.25 (± 0.08)	
Change at Week 36; n=88, 93, 48	0.49 (± 0.09)	0.18 (± 0.06)	0.20 (± 0.08)	
Change at Week 48; n=83, 90, 47	0.40 (± 0.07)	0.19 (± 0.04)	0.21 (± 0.11)	

Notes:

[20] - n=observed cases at given timepoint

[21] - n=observed cases at given timepoint

[22] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change at Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.2

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change at Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.15

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.13

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Change at Week 48	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.12

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

Change at Week 48

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.08

Secondary: Clinical Disease Activity Index (CDAI) at All Measured Timepoints

End point title	Clinical Disease Activity Index (CDAI) at All Measured Timepoints

End point description:

The CDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, and Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable. The CDAI score ranges from 0 to 76, where a higher score represents worse disease.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:
Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[23]	101[24]	51[25]	
Units: score on a scale				
arithmetic mean (standard error)				
Baseline; n=101, 101, 51	1.01 (± 0.10)	0.92 (± 0.13)	0.71 (± 0.12)	
Week 12; n=100, 101, 51	6.42 (± 0.98)	4.08 (± 0.74)	3.95 (± 1.20)	
Week 24; n=92, 96, 49	5.07 (± 0.95)	4.63 (± 0.91)	2.35 (± 0.60)	
Week 36; n=89, 93, 48	3.60 (± 0.63)	1.93 (± 0.36)	2.04 (± 0.41)	
Week 48; n=85, 92, 47	3.06 (± 0.38)	2.00 (± 0.23)	2.61 (± 0.91)	

Notes:
[23] - n=observed cases at given timepoint
[24] - n=observed cases at given timepoint
[25] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.16

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	1.62

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.76
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	1.23

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.95
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	1.38

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	2.15
Variability estimate	Standard error of the mean
Dispersion value	1.32

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	0.9

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.72

Statistical analysis title	Statistical Analysis 9
Statistical analysis description: Week 48	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.43
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.44

Secondary: Change From Baseline in CDAI at All Measured Timepoints

End point title	Change From Baseline in CDAI at All Measured Timepoints

End point description:

The CDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, and Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable. The CDAI score ranges from 0 to 76, where a higher score represents worse disease. A negative change from baseline indicates improvement.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:
Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[26]	101[27]	51[28]	
Units: score on a scale				
arithmetic mean (standard error)				
Change at Week 12; n=100, 101, 51	5.39 (± 0.97)	3.15 (± 0.73)	3.24 (± 1.17)	
Change at Week 24; n=92, 96, 49	4.09 (± 0.95)	3.75 (± 0.90)	1.70 (± 0.61)	
Change at Week 36; n=89, 93, 48	2.69 (± 0.63)	1.07 (± 0.37)	1.41 (± 0.40)	
Change at Week 48; n=85, 92, 47	2.17 (± 0.37)	1.15 (± 0.23)	2.00 (± 0.92)	

Notes:
[26] - n=observed cases at given timepoint
[27] - n=observed cases at given timepoint
[28] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change at Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.29
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	1.59

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change at Week 12	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.63
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	1.21

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.62
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	1.37

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Change at Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.91
upper limit	2.23
Variability estimate	Standard error of the mean
Dispersion value	1.3

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Change at Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.72

Statistical analysis title	Statistical Analysis 7
Statistical analysis description: Change at Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	1.81
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Statistical Analysis 8
Statistical analysis description: Change at Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	two sample t-test
Parameter estimate	Treatment Difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.88
upper limit	-0.16
Variability estimate	Standard error of the mean
Dispersion value	0.43

Secondary: Percentage of Participants With SDAI Remission (≤ 3.3) at All Measured Timepoints

End point title	Percentage of Participants With SDAI Remission (≤ 3.3) at All Measured Timepoints

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Primary Analysis Set: all randomized participants. Observed cases at given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[29]	101[30]	51[31]	
Units: percentage of participants				
number (not applicable)				
Baseline; n=100, 101, 51	96.0	92.1	96.1	
Week 12; n=100, 100, 51	50.0	64.0	74.5	
Week 24; n=98, 99, 50	38.8	56.6	62.0	
Week 36; n=97, 99, 49	36.1	55.6	55.1	
Week 48; n=95, 96, 48	30.5	52.1	56.3	

Notes:

[29] - n=observed cases at given time point

[30] - n=observed cases at given time point

[31] - n=observed cases at given time point

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Baseline	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [32]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	6.6
Variability estimate	Standard error of the mean
Dispersion value	3.4

Notes:

[32] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Baseline

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [33]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	3.3

Notes:

[33] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	9
upper limit	40
Variability estimate	Standard error of the mean
Dispersion value	7.9

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.063 [34]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	27.6
Variability estimate	Standard error of the mean
Dispersion value	6.9

Notes:

[34] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 24

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.7
upper limit	39.8
Variability estimate	Standard error of the mean
Dispersion value	8.4

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Week 24

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [35]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	31.5
Variability estimate	Standard error of the mean
Dispersion value	7

Notes:

[35] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	35.9
Variability estimate	Standard error of the mean
Dispersion value	8.6

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	19.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.8
upper limit	33.2
Variability estimate	Standard error of the mean
Dispersion value	7

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [36]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	25.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.9
upper limit	42.5
Variability estimate	Standard error of the mean
Dispersion value	8.6

Notes:

[36] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
Week 48	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [37]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.9
upper limit	35.2
Variability estimate	Standard error of the mean
Dispersion value	7

Notes:

[37] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Secondary: Percentage of Participants With Boolean Remission at All Measured Timepoints

End point title	Percentage of Participants With Boolean Remission at All Measured Timepoints

End point description:

A participant achieves Boolean remission (66/68-joint count) if all of the following criteria are met at a single timepoint:
- 68-joint tender joint count ≤ 1
- 66-joint swollen joint count ≤ 1
- CRP (mg/dL) ≤ 1
- Patient's Global Assessment of Disease Activity using a VAS (where 0=no arthritis activity at all and 10=worst arthritis activity imaginable) ≤ 1.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[38]	101[39]	51[40]	
Units: percentage of participants				
number (not applicable)				
Baseline; n=100, 101, 51	34.0	34.7	45.1	
Week 12; n=100, 100, 51	18.0	23.0	19.6	
Week 24; n=92, 96, 49	15.2	16.7	26.5	
Week 36; n=89, 93, 48	14.6	20.4	27.1	
Week 48; n=84, 90, 47	20.2	13.3	25.5	

Notes:

[38] - n=observed cases at given timepoint

[39] - n=observed cases at given timepoint

[40] - n=observed cases at given timepoint

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Baseline

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [41]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	27.6
Variability estimate	Standard error of the mean
Dispersion value	8.4

Notes:

[41] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Baseline

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [42]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.5
upper limit	13.8
Variability estimate	Standard error of the mean
Dispersion value	6.7

Notes:

[42] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [43]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	14.9
Variability estimate	Standard error of the mean
Dispersion value	6.8

Notes:

[43] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Week 12

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48 [44]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	16.2
Variability estimate	Standard error of the mean
Dispersion value	5.7

Notes:

[44] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Week 24

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16 [45]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	25.7
Variability estimate	Standard error of the mean
Dispersion value	7.3

Notes:

[45] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Week 24	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [46]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	11.9
Variability estimate	Standard error of the mean
Dispersion value	5.3

Notes:

[46] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Week 36	
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [47]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	27
Variability estimate	Standard error of the mean
Dispersion value	7.4

Notes:

[47] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Week 36	

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4 [48]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	16.8
Variability estimate	Standard error of the mean
Dispersion value	5.6

Notes:

[48] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

Week 48

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.63 [49]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	20.4
Variability estimate	Standard error of the mean
Dispersion value	7.7

Notes:

[49] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

Week 48

Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [50]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	5.7

Notes:

[50] - The risk difference and its p-value were estimated from the Chi-squared test with continuity correction.

Secondary: Percentage of Participants With Disease Worsening

End point title	Percentage of Participants With Disease Worsening

End point description:

Disease worsening is defined as any of the following:
- an SDAI > 3.3 and ≤ 11 during 2 consecutive visits at least 2 weeks apart
- SDAI > 3.3 and ≤ 11 on 3 or more separate visits
- SDAI > 11 after randomization.

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Primary Analysis Set: all randomized participants. Observed cases at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 36 and Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101[51]	101[52]	51[53]	
Units: percentage of participants				
number (not applicable)				
Baseline; n=100, 101, 51	0.0	0.0	0.0	
Week 12; n=100, 100, 51	42.0	23.0	17.6	
Week 24; n=92, 96, 49	8.7	14.6	6.1	
Week 36; n=89, 93, 48	10.1	3.2	8.3	
Week 48; n=84, 90, 47	4.8	0.0	4.3	

Notes:

[51] - n=observed cases at given timepoint

[52] - n=observed cases at given timepoint

[53] - n=observed cases at given timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Worsening

End point title	Time to Disease Worsening

End point description:

Disease worsening is defined as any of the following:
- an SDAI > 3.3 and ≤ 11 during 2 consecutive visits at least 2 weeks apart
- SDAI > 3.3 and ≤ 11 on 3 or more separate visits
- SDAI > 11 after randomization.

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Primary Analysis Set: all randomized participants. Participants with disease worsening.

End point type	Secondary

End point timeframe:

up to Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	40	18	
Units: weeks				
arithmetic mean (standard error)	17.22 (± 1.70)	17.14 (± 1.45)	23.16 (± 3.22)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [54]
Method	Logrank

Notes:

[54] - P-value was based on the Log-rank test for overall difference on disease-worsening event between two groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [55]
Method	Logrank

Notes:

[55] - P-value was based on the Log-rank test for overall difference on disease-worsening event between two groups.

Secondary: Time to Recapture SDAI Remission After Starting Rescue Treatment

End point title	Time to Recapture SDAI Remission After Starting Rescue Treatment

End point description:

In participants who receive rescue treatment during the double-blind treatment period.

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Rescue Analysis Set: randomized participants who met the definition of disease-worsening and received both at least 1 dose of active rescue therapy etanercept and at least 1 dose of active rescue therapy methotrexate. Participants who recaptured SDAI remission. Observed cases.

End point type	Secondary

End point timeframe:

Between rescue and remission or Week 48, whichever comes first.

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	27	12	
Units: weeks				
arithmetic mean (standard error)	13.42 (± 1.55)	15.70 (± 1.37)	13.38 (± 2.19)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [56]
Method	Logrank

Notes:

[56] - P-value was based on the Log-rank test for overall difference on disease-worsening event between two groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept Monotherapy
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51 [57]
Method	Logrank

Notes:

[57] - P-value was based on the Log-rank test for overall difference on disease-worsening event between two groups.

Secondary: Percentage of Participants Receiving Rescue Treatment Who Experienced SDAI Remission at Week 48

End point title	Percentage of Participants Receiving Rescue Treatment Who Experienced SDAI Remission at Week 48

End point description:

The SDAI is a composite score that is based on the number of tender and swollen joints using a 28-joint count, Physician's Global Assessment of Disease Activity using a visual analog scale (VAS) where 0=no activity at all and 100=worst activity imaginable, Patient's Global Assessment of Disease Activity using a VAS where 0=no arthritis activity at all and 100=worst arthritis activity imaginable, and C-reactive protein (CRP) in mg/dL. The SDAI score ranges from 0 to 86, with higher scores representing worse disease. SDAI remission was defined as a score of ≤ 3.3.

Rescue Analysis Set: randomized participants who met the definition of disease-worsening and received both at least 1 dose of active rescue therapy etanercept and at least 1 dose of active rescue therapy methotrexate. Observed cases.

End point type	Secondary

End point timeframe:

Week 48

End point values	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy	Double-Blind Treatment: Etanercept plus Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	34	15	
Units: percentage of participants				
number (not applicable)	54.2	55.9	66.7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Treatment: Methotrexate Monotherapy v Double-Blind Treatment: Etanercept plus Methotrexate
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	40.2
Variability estimate	Standard error of the mean
Dispersion value	14.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Open-Label Run-In period: from enrollment up to 24 weeks. Double-Blind Treatment period: from randomization up to 48 weeks plus 30 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Open Label Run-In: Etanercept plus Methotrexate

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 24 weeks. Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Methotrexate Monotherapy

Reporting group description:

Oral methotrexate 10 to 25 mg weekly plus placebo for etanercept for 48 weeks. Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Etanercept Monotherapy

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus placebo to methotrexate for 48 weeks. Participants also receive folic acid as standard of care.

Reporting group title	Double-Blind Treatment: Etanercept plus Methotrexate

Reporting group description:

Etanercept 50 mg weekly by subcutaneous injection plus oral methotrexate 10 to 25 mg weekly for 48 weeks. Participants also receive folic acid as standard of care.

Reporting group title	Open Label Rescue: Etanercept plus Methotrexate

Reporting group description:

After randomization, a participant experiencing protocol-defined disease worsening initiated rescue treatment with etanercept 50 mg QW plus methotrexate (10 to 25 mg).

Serious adverse events	Open Label Run-In: Etanercept plus Methotrexate	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 368 (3.80%)	3 / 100 (3.00%)	3 / 99 (3.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Prostate cancer stage III			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Small cell lung cancer			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic pseudoaneurysm			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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

Carpal tunnel syndrome			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 368 (0.54%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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			
Cholecystitis			
subjects affected / exposed	0 / 368 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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			
Arthritis reactive			
subjects affected / exposed	0 / 368 (0.00%)	1 / 100 (1.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	1 / 99 (1.01%)
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			
Herpes zoster			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 368 (0.54%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Abscess of salivary gland			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Cellulitis			
subjects affected / exposed	1 / 368 (0.27%)	0 / 100 (0.00%)	0 / 99 (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
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 368 (0.00%)	0 / 100 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Treatment: Etanercept plus Methotrexate	Open Label Rescue: Etanercept plus Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 53 (3.77%)	4 / 103 (3.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage III			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 53 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic pseudoaneurysm			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess intestinal			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of salivary gland			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Open Label Run-In: Etanercept plus Methotrexate	Double-Blind Treatment: Methotrexate Monotherapy	Double-Blind Treatment: Etanercept Monotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 368 (7.88%)	21 / 100 (21.00%)	12 / 99 (12.12%)
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	3 / 368 (0.82%)	18 / 100 (18.00%)	7 / 99 (7.07%)
occurrences (all)	3	19	7
Infections and infestations			
Bronchitis			

subjects affected / exposed	6 / 368 (1.63%)	0 / 100 (0.00%)	3 / 99 (3.03%)
occurrences (all)	6	0	3
Upper respiratory tract infection			
subjects affected / exposed	20 / 368 (5.43%)	3 / 100 (3.00%)	3 / 99 (3.03%)
occurrences (all)	20	4	5

Non-serious adverse events	Double-Blind Treatment: Etanercept plus Methotrexate	Open Label Rescue: Etanercept plus Methotrexate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 53 (15.09%)	9 / 103 (8.74%)	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	3 / 53 (5.66%)	2 / 103 (1.94%)	
occurrences (all)	3	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 53 (7.55%)	0 / 103 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 53 (1.89%)	7 / 103 (6.80%)	
occurrences (all)	1	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2015	- Provided clarification for reporting hepatotoxicity as a serious adverse event - Clarified indications regarding use of etanercept in the United States and Canada, and added medical information phone number as a reference for countries other than United States and Canada - Provided clarification for inclusion criteria for etanercept use, specifying the dose - Provided clarification for inclusion criteria for methotrexate use, accommodating conversion from SC to oral route and provided clarification regarding formulation of methotrexate - Provided clarifications regarding joint assessments, to strengthen wording related to continuity of assessors in the study, and allowing for assessments by principal investigators - Provided updates throughout to reflect the number of global participating sites - Added the EudraCT number - Added medical information phone number as a reference for countries other than United States and Canada
08 July 2015	- Provided updated pregnancy and contraception language.
30 October 2015	- Updated to be consistent with international regulations and requirements.
03 November 2016	- Updated clinical hypothesis to align with the primary objective of the study. - Updated CTCAE grading version to 4.0 to reflect the most recent version. - Updated inclusion and exclusion criteria to decrease the stringency of subject eligibility. - Reduced study sample size due to adjustments in estimated effect sizes for treatment groups. - Removed prior use of a biologic agent as a covariate influencing primary and secondary endpoints. - Removed sequential testing to align with the updated clinical hypothesis.
20 December 2016	- Reduced strictness of subject re-screening criteria.
17 October 2017	- Reduced study sample size due to adjustments in estimated effect sizes for treatment groups.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported