Clinical trial results:
A Phase IV Registry of Etanercept in Children With Juvenile Rheumatoid Arthritis

Summary

EudraCT number	2012-001171-37
Trial protocol	Outside EU/EEA
Global end of trial date	31 January 2008

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	20021626

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00078793
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	Amgen Medical Information, Amgen, 001 8007726436, medinfo@amgen.com
Scientific contact	Amgen Medical Information, Amgen, 001 8007726436, medinfo@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000029-PIP01-08
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	31 January 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the long-term safety of etanercept administered with or without other disease-modifying anti-rheumatic drugs (DMARDS) in pediatric subjects with polyarticular course or systemic juvenile rheumatoid arthritis (JRA) compared to a control cohort of subjects with polyarticular course or systemic JRA receiving methotrexate (with or without other DMARDS).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH), and Good Clinical Practice (GCP) regulations/guidelines.
All subjects, or their legally acceptable guardian/representative, provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and the sponsor received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2000
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	United States: 563
Country: Number of subjects enrolled	Canada: 31
Worldwide total number of subjects	594
EEA total number of subjects	0

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	3

months)	
Children (2-11 years)	353
Adolescents (12-17 years)	227
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was a multicenter registry utilizing study sites from the Pediatric Rheumatology Collaborative Study Group (PRCSG) in the United States and Canada.

Pre-assignment

Screening details:

Boys or girls age 2 to 18 years (inclusive) with a diagnosis of systemic, polyarticular, or pauciarticular JRA defined by the American College of Rheumatology (ACR) criteria.
This was a non-randomized study. Subjects who satisfied all eligibility criteria were enrolled into 1 of 3 cohorts in the study based on their baseline treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Methotrexate Only

Arm description:

Subjects received methotrexate at a minimum dose of 10 mg/m²/week.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Parenteral use

Dosage and administration details:

Subjects received methotrexate at a minimum dose of 10 mg/m²/week (~ 0.3 mg/kg/week, maximum dose of 1 mg/kg/week).

Arm title	Etanercept Only

Arm description:

Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg.

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

Dosage and administration details:

Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg (maximum dose of 50 mg/week).

Arm title	Etanercept + Methotrexate

Arm description:

Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg and methotrexate at a minimum dose of 10 mg/m²/week.

Arm type	Experimental

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Parenteral use

Dosage and administration details:

Subjects received methotrexate at a minimum dose of 10 mg/m²/week (~ 0.3 mg/kg/week, maximum dose of 1 mg/kg/week).

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

Dosage and administration details:

Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg (maximum dose of 50 mg/week).

Number of subjects in period 1	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate
Started	197	103	294
Completed	66	47	132
Not completed	131	56	162
Physician decision	4	3	4
Insufficient therapeutic effect	36	8	59
Other	30	16	48
Adverse event	3	2	1
Refusal - subject	8	4	13
Remission	24	8	12
Refusal - parent/guardian	9	5	11
Protocol deviation	17	10	14

Baseline characteristics

Reporting groups	
Reporting group title	Methotrexate Only
Reporting group description:	
Subjects received methotrexate at a minimum dose of 10 mg/m²/week.	
Reporting group title	Etanercept Only
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg.	
Reporting group title	Etanercept + Methotrexate
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg and methotrexate at a minimum dose of 10 mg/m²/week.	

Reporting group values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate
Number of subjects	197	103	294
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.02	10.78	10.09
standard deviation	± 4.4	± 4.1	± 4.69
Gender categorical Units: Subjects			
Female	145	83	214
Male	52	20	80
Race Units: Subjects			
Asian	1	4	6
African American	12	5	29
Caucasian	151	78	214
Hispanic	24	7	29
Native American	0	1	1
Other	9	8	15
JRA Disease Duration Units: months			
arithmetic mean	20.15	58.11	40.66
standard deviation	± 30.69	± 44.53	± 41.68
Height Units: cm			
arithmetic mean	133.02	141.19	137.2
standard deviation	± 25.29	± 22.79	± 26.23
Weight Units: kg			
arithmetic mean	37.18	42.68	40.14
standard deviation	± 20.82	± 22.82	± 21.84

Reporting group values	Total		

Number of subjects	594		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	442		
Male	152		
Race Units: Subjects			
Asian	11		
African American	46		
Caucasian	443		
Hispanic	60		
Native American	2		
Other	32		
JRA Disease Duration Units: months arithmetic mean standard deviation	- -		
Height Units: cm arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Methotrexate Only
Reporting group description:	
Subjects received methotrexate at a minimum dose of 10 mg/m²/week.	
Reporting group title	Etanercept Only
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg.	
Reporting group title	Etanercept + Methotrexate
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg and methotrexate at a minimum dose of 10 mg/m²/week.	
Subject analysis set title	Methotrexate: Age ≤ 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects ≤ 4 years of age who received methotrexate only.	
Subject analysis set title	Etanercept: Age ≤ 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects ≤ 4 years of age who received etanercept only.	
Subject analysis set title	Etanercept+MTX: Age ≤ 4
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects ≤ 4 years old who received etanercept and methotrexate.	
Subject analysis set title	Methotrexate: Age 5-7
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 5-7 years old who received methotrexate only.	
Subject analysis set title	Etanercept: Age 5-7
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 5-7 years old who received etanercept only.	
Subject analysis set title	Etanercept+MTX: Age 5-7
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 5-7 years old who received etanercept and methotrexate.	
Subject analysis set title	Methotrexate: Age 8-12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 8-12 years old who received methotrexate only.	
Subject analysis set title	Etanercept: Age 8-12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 8-12 years old who received etanercept only.	
Subject analysis set title	Etanercept+MTX: Age 8-12
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects 8-12 years old who received etanercept and methotrexate	
Subject analysis set title	Methotrexate: Age 13-18
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects 13-18 years old who received methotrexate only.

Subject analysis set title	Etanercept: Age 13-18
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects 13-18 years old who received etanercept only.

Subject analysis set title	Etanercept+MTX: Age 13-18
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects 13-18 years old who received etanercept and methotrexate.

Primary: Number of subjects with adverse events

End point title	Number of subjects with adverse events

End point description:

The severity grading scale used in this study was common toxicity criteria (CTC) version 2.0.

End point type	Primary

End point timeframe:

36 months

End point values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197	103	294	
Units: subjects				
Any adverse event	43	26	78	
Infectious episodes	4	4	11	
AEs leading to withdrawal from drug	5	1	9	
Serious adverse events	14	9	28	
Medically important infections	4	4	11	
Death	0	0	0	
Autoimmune diseases	15	8	13	
Grade 3 or 4 adverse events	13	11	29	
Cancers	0	0	0	

Statistical analyses

Statistical analysis title	Any Adverse Events

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2242
Method	Regression, Logistic

Statistical analysis title	Infectious Episodes

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3004
Method	Regression, Logistic

Statistical analysis title	AEs Leading to Withdrawal from Drug

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5794
Method	Regression, Logistic

Statistical analysis title	Serious Adverse Events

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4384
Method	Regression, Logistic

Statistical analysis title	Medically Important Infections

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3004
Method	Regression, Logistic

Statistical analysis title	Autoimmune Diseases

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.675
Method	Regression, Logistic

Statistical analysis title	Grade 3 and 4 Adverse Events

Statistical analysis description:

Comparison of event rates of methotrexate only versus etanercept only or etanercept and methotrexate using logistic regression adjusted for age, sex, baseline disease characteristics and treatment crossover.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1827
Method	Regression, Logistic

Secondary: Change From Baseline in Height Percentile

End point title	Change From Baseline in Height Percentile

End point description:

End point type	Secondary

End point timeframe:

Baseline, Year 1, Year 2, Year 3 and Last Visit

End point values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197[1]	103[2]	294[3]	
Units: percentile				
arithmetic mean (standard deviation)				
Year 1 (n=121, 69, 215)	-0.21 (± 10.58)	1.21 (± 11.86)	2.36 (± 9.3)	
Year 2 (n=91, 48, 151)	-0.95 (± 13.78)	2.8 (± 15.11)	3.29 (± 12.61)	
Year 3 (n=62, 44, 120)	-2.38 (± 16.75)	4.8 (± 17.24)	5.58 (± 15.76)	
Last Visit (n=186, 95, 269)	-1.56 (± 14.98)	2.64 (± 13.77)	2.36 (± 14.31)	

Notes:

[1] - Enrolled subjects who completed at least 1 evaluation while on drug

[2] - Enrolled subjects who completed at least 1 evaluation while on drug

[3] - Enrolled subjects who completed at least 1 evaluation while on drug

Statistical analyses

Statistical analysis title	Year 1

Statistical analysis description:

Comparison of mean percentile change in height in methotrexate alone versus etanercept alone or etanercpt plus methotrexate

Comparison groups	Etanercept Only v Etanercept + Methotrexate v Methotrexate Only
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0497
Method	ANCOVA

Statistical analysis title	Year 2

Statistical analysis description:

Comparison of mean percentile change in height in methotrexate alone versus etanercept alone or etanercpt plus methotrexate

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANCOVA

Statistical analysis title	Year 3

Statistical analysis description:

Comparison of mean percentile change in height in methotrexate alone versus etanercept alone or etanercpt plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept +

	Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	ANCOVA

Statistical analysis title	Last Visit

Statistical analysis description:

Comparison of mean percentile change in height in methotrexate alone versus etanercept alone or etanercpt plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0049
Method	ANCOVA

Secondary: Change From Baseline in Weight Percentile

End point title	Change From Baseline in Weight Percentile

End point description:

End point type	Secondary

End point timeframe:

Baseline, Year 1, Year 2, Year 3 and Last Visit

End point values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	197[4]	103[5]	294[6]	
Units: percentile				
arithmetic mean (standard deviation)				
Year 1 (n=122, 71, 218)	1.59 (± 14.02)	7.44 (± 12.85)	2.91 (± 13.52)	
Year 2 (n=92, 48, 152)	1.55 (± 11.25)	9.97 (± 16.96)	6.93 (± 14.99)	
Year 3 (n=64, 44, 122)	-1.4 (± 15.2)	13.01 (± 20.88)	8.38 (± 16.42)	
Last Visit (n=189, 98, 272)	0.98 (± 14.27)	5.9 (± 18.83)	4.05 (± 16.12)	

Notes:

[4] - Enrolled subjects completing at least 1 evaluation while on drug

[5] - Enrolled subjects completing at least 1 evaluation while on drug

[6] - Enrolled subjects completing at least 1 evaluation while on drug

Statistical analyses

Statistical analysis title	Year 1

Statistical analysis description:

Comparison of mean percentile change in weight in methotrexate only versus etanercept only or etanercept plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2975
Method	ANCOVA

Statistical analysis title	Year 2

Statistical analysis description:

Comparison of mean percentile change in weight in methotrexate only versus etanercept only or etanercept plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	ANCOVA

Statistical analysis title	Year 3

Statistical analysis description:

Comparison of mean percentile change in weight in methotrexate only versus etanercept only or etanercept plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA

Statistical analysis title	Last Visit

Statistical analysis description:

Comparison of mean percentile change in weight in methotrexate only versus etanercept only or etanercept plus methotrexate.

Comparison groups	Methotrexate Only v Etanercept Only v Etanercept + Methotrexate

Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041
Method	ANCOVA

Secondary: Tanner Stage Assessment by Age Group Over Time

End point title	Tanner Stage Assessment by Age Group Over Time

End point description:

Tanner assessment scores document the stage of development of secondary sexual characteristics. Female pubertal development staged by breast size; male pubertal development staged by size of the external genitalia. Rated in 5 stages: stage 1 (prepubertal) to 5 (adult-like development).
"n" indicates the number of subjects with available data in each age and treatment group at each time point. Please note that for the Etanercept: Age ≤ 4 group, standard deviation could not be calculated for Month 6 and Month 24 due to a sample size of 1.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30 and 36

End point values	Methotrexate: Age ≤ 4	Etanercept: Age ≤ 4	Etanercept+MTX: Age ≤ 4	Methotrexate: Age 5-7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	9	47	41
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,29,19,10,31)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 6 (n=14,1,15,19,4,18,22,13,25,13,7,30)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 12 (n=11,3,13,19,5,14,20,12,24,9,7,25)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 24 (=8,1,11,14,3,15,16,8,19,7,5,15)	1 (± 0)	1 (± 0)	1 (± 0)	1.1 (± 0.4)
Month 30 (n=5,2,8,10,2,12,11,8,16,5,5,13)	1 (± 0)	1 (± 0)	1 (± 0)	1.2 (± 0.4)
Month 36 (=4,2,8,6,3,11,9,6,13,5,4,15)	1 (± 0)	1 (± 0)	1 (± 0)	1.3 (± 0.5)

End point values	Etanercept: Age 5-7	Etanercept+MTX: Age 5-7	Methotrexate: Age 8-12	Etanercept: Age 8-12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	56	66	41
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,29,19,10,31)	1 (± 0)	1 (± 0)	1.6 (± 0.8)	1.6 (± 1.2)

Month 6 (n=14,1,15,19,4,18,22,13,25,13,7,30)	1 (± 0)	1 (± 0)	2.2 (± 1.4)	1.6 (± 1)
Month 12 (n=11,3,13,19,5,14,20,12,24,9,7,25)	1.2 (± 0.4)	1 (± 0)	2.5 (± 1.5)	1.6 (± 1)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	1 (± 0)	1 (± 0)	2.4 (± 1.4)	1.8 (± 1.1)
Month 24 (=8,1,11,14,3,15,16,8,19,7,5,15)	1 (± 0)	1.1 (± 0.4)	2.8 (± 1.6)	2 (± 1.1)
Month 30 (n=5,2,8,10,2,12,11,8,16,5,5,13)	1.5 (± 0.7)	1.1 (± 0.3)	2.9 (± 1.6)	2.6 (± 1.3)
Month 36 (=4,2,8,6,3,11,9,6,13,5,4,15)	1.3 (± 0.6)	1.5 (± 0.5)	3.3 (± 1.7)	2.5 (± 1.4)

End point values	Etanercept+MTX: Age 8-12	Methotrexate: Age 13-18	Etanercept: Age 13-18	Etanercept+MTX: Age 13-18
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	85	52	38	106
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,29,19,10,31)	1.7 (± 1.1)	4.2 (± 1.1)	4.2 (± 0.8)	4.4 (± 0.8)
Month 6 (n=14,1,15,19,4,18,22,13,25,13,7,30)	1.9 (± 1.2)	4.4 (± 1)	4.6 (± 0.5)	4.3 (± 0.9)
Month 12 (n=11,3,13,19,5,14,20,12,24,9,7,25)	2.6 (± 1.3)	4.3 (± 1.1)	4.7 (± 0.5)	4.4 (± 0.6)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	2.8 (± 1.5)	4.8 (± 0.5)	4.8 (± 0.5)	4.5 (± 0.7)
Month 24 (=8,1,11,14,3,15,16,8,19,7,5,15)	3.1 (± 1.4)	4.7 (± 0.5)	4.8 (± 0.4)	4.6 (± 0.6)
Month 30 (n=5,2,8,10,2,12,11,8,16,5,5,13)	3.3 (± 1.4)	4.6 (± 0.5)	4.8 (± 0.4)	4.8 (± 0.4)
Month 36 (=4,2,8,6,3,11,9,6,13,5,4,15)	3.4 (± 1.2)	4.6 (± 0.5)	5 (± 0)	4.8 (± 0.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Tanner Pubic Stage Assessment by Age Over Time

End point title	Tanner Pubic Stage Assessment by Age Over Time

End point description:

The Tanner pubic hair scale ranges from stage 1 (no pubic hair at all; prepubertal state) to stage 5 (hair extends to medial surface of the thighs.
"n" indicates the number of subjects with available data in each age and treatment group at each time point.
Note that the standard deviation could not be calculated for the Etanercept: Age ≤ 4 group at Month 6 and Month 24 as the sample size was 1.

End point type	Secondary

End point timeframe:

Baseline and Months 6, 12, 18, 24, 30 and 36

End point values	Methotrexate: Age ≤ 4	Etanercept: Age ≤ 4	Etanercept+MTX: Age ≤ 4	Methotrexate: Age 5-7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	9	47	41
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,28,19,10,31)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 6 (n=14,1,15,19,4,18,23,14,25,13,7,30)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 12 (n=11,3,13,19,5,14,20,12,23,9,7,26)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 24 (n=8,1,11,14,3,15,15,8,19,7,5,15)	1 (± 0)	1 (± 0)	1 (± 0)	1 (± 0)
Month 30 (n=5,2,8,10,2,12,12,8,17,5,5,13)	1 (± 0)	1 (± 0)	1 (± 0)	1.1 (± 0.3)
Month 36 (n=4,2,8,6,3,11,9,6,13,5,4,15)	1 (± 0)	1 (± 0)	1 (± 0)	1.3 (± 0.5)

End point values	Etanercept: Age 5-7	Etanercept+MTX: Age 5-7	Methotrexate: Age 8-12	Etanercept: Age 8-12
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	56	66	41
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,28,19,10,31)	1 (± 0)	1 (± 0)	1.6 (± 0.8)	1.6 (± 1.2)
Month 6 (n=14,1,15,19,4,18,23,14,25,13,7,30)	1 (± 0)	1 (± 0)	2.1 (± 0.4)	1.6 (± 1.1)
Month 12 (n=11,3,13,19,5,14,20,12,23,9,7,26)	1.2 (± 0.4)	1 (± 0)	2.4 (± 1.5)	1.7 (± 1.1)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	1 (± 0)	1.1 (± 0.3)	2.5 (± 1.4)	1.7 (± 1.1)
Month 24 (n=8,1,11,14,3,15,15,8,19,7,5,15)	1 (± 0)	1.1 (± 0.3)	2.9 (± 1.5)	1.8 (± 1)
Month 30 (n=5,2,8,10,2,12,12,8,17,5,5,13)	1 (± 0)	1.2 (± 0.4)	3 (± 1.4)	2.5 (± 1.3)
Month 36 (n=4,2,8,6,3,11,9,6,13,5,4,15)	1 (± 0)	1.1 (± 0.3)	3.3 (± 1.7)	2.7 (± 1.6)

End point values	Etanercept+MTX: Age 8-12	Methotrexate: Age 13-18	Etanercept: Age 13-18	Etanercept+MTX: Age 13-18
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	85	52	38	106
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=20,3,19,20,6,24,33,14,28,19,10,31)	1.6 (± 1)	4.4 (± 1)	4.1 (± 1.1)	4.4 (± 0.8)
Month 6 (n=14,1,15,19,4,18,23,14,25,13,7,30)	2 (± 1.2)	4.4 (± 1.2)	4.6 (± 0.5)	4.3 (± 0.9)

Month 12 (n=11,3,13,19,5,14,20,12,23,9,7,26)	2.4 (± 1.4)	4.3 (± 1.1)	4.6 (± 0.5)	4.5 (± 0.6)
Month 18 (n=7,3,10,16,5,14,17,9,20,8,4,21)	2.7 (± 1.5)	4.8 (± 0.5)	4.8 (± 0.5)	4.4 (± 0.9)
Month 24 (n=8,1,11,14,3,15,15,8,19,7,5,15)	3.1 (± 1.4)	4.7 (± 0.5)	4.8 (± 0.4)	4.5 (± 0.6)
Month 30 (n=5,2,8,10,2,12,12,8,17,5,5,13)	3.2 (± 1.4)	4.8 (± 0.4)	4.8 (± 0.4)	4.7 (± 0.5)
Month 36 (n=4,2,8,6,3,11,9,6,13,5,4,15)	3.3 (± 1.3)	4.8 (± 0.4)	5 (± 0)	4.7 (± 0.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Child Behavior Checklist (Ages 4 to 18) Total Problem Score Over Time

End point title	Child Behavior Checklist (Ages 4 to 18) Total Problem Score Over Time

End point description:

The Child Behavior Checklist (CBCL) is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
For subjects 4 to 18 years old the checklist consists of 110 single-item questions and one 8-item question including the following behaviors: withdrawn, somatic problems, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior, sex problems, and other problems. Each question is scored on a three-point Likert scale (0=absent, 1= occurs sometimes, 2=occurs often).
The total score is obtained by adding responses to all questions (excluding question on asthma and allergy); the range of the total score is 0 to 236 (worst).

End point type	Secondary

End point timeframe:

Baseline, and Months 3, 6, 9, 12, 18, 24, 30, and 36

End point values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	162	91	248	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=162, 91, 248)	21.85 (± 16.44)	17.56 (± 16.97)	20.5 (± 17.89)	
Month 3 (n=145, 81, 232)	16.04 (± 13.3)	15.94 (± 17)	16.38 (± 14.41)	
Month 6 (n=123, 76, 212)	15.74 (± 14.96)	16.88 (± 19.57)	15.61 (± 16.3)	
Month 9 (n=109, 68, 196)	14.21 (± 14.54)	12.85 (± 14.66)	14.78 (± 15.28)	
Month 12 (n=108, 65, 198)	14.25 (± 13.77)	13.43 (± 18.13)	14.43 (± 14.24)	
Month 18 (n=98, 56, 166)	13.02 (± 14.43)	14.21 (± 17.3)	14.45 (± 14.57)	
Month 24 (n=88, 46, 139)	11.89 (± 13.49)	14.87 (± 13.99)	15.71 (± 17.72)	

Month 30 (n=68, 43, 133)	12.79 (± 13.92)	15.84 (± 16.41)	14.38 (± 15.12)	
Month 36/Early Discontinuation (n=141, 75, 210)	13.47 (± 14.04)	13.35 (± 14.85)	14.92 (± 15.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Child Behavior Checklist (Ages 2 to 3) Total Problem Score Over Time

End point title	Child Behavior Checklist (Ages 2 to 3) Total Problem Score Over Time

End point description:

The Child Behavior Checklist (CBCL) is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. For subjects 2 to 3 years old the checklist consists of 100 single-item questions including the following behaviors: anxious/depressed, withdrawn, sleep problems, somatic problems, aggressive behavior, destructive behavior, and other problems. Each question is scored on a three-point Likert scale (0=absent, 1= occurs sometimes, 2=occurs often). The total score is obtained by adding responses to all questions; the range of the total score is 0 to 200 (worst).
"0" indicates values that could not be calculated due to a sample size of 0 or 1.

End point type	Secondary

End point timeframe:

Baseline and Months 3, 6, 9, 12, 18, 24, and 36

End point values	Methotrexate Only	Etanercept Only	Etanercept + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	6	28	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=25, 6, 28)	36.32 (± 21.36)	38.33 (± 16.98)	32.25 (± 20.58)	
Month 3 (n=16, 6, 18)	34.69 (± 24.24)	30.5 (± 17.69)	30.61 (± 23.63)	
Month 6 (n=10, 4, 15)	29.9 (± 11.99)	23.75 (± 17.08)	31.27 (± 24.85)	
Month 9 (n=12, 1, 7)	27.58 (± 20.97)	52 (± 0)	25.43 (± 15.75)	
Month 12 (n=8, 0, 8)	17.88 (± 14.13)	0 (± 0)	26 (± 15)	
Month 18 (n=5, 0, 4)	7.8 (± 7.85)	0 (± 0)	33.25 (± 25.05)	
Month 24 (n=0, 0, 3)	0 (± 0)	0 (± 0)	25.67 (± 18.9)	
Month 36/Early Discontinuation (n=5, 2, 3)	39.8 (± 33.51)	29 (± 2.83)	61.67 (± 16.56)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
36 months	
Adverse event reporting additional description:	
Enbrel Protocol 20021626	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.1

Reporting groups	
Reporting group title	Methotrexate Only
Reporting group description:	
Subjects received methotrexate at a minimum dose of 10 mg/m²/week.	
Reporting group title	Etanercept + Methotrexate
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg and methotrexate at a minimum dose of 10 mg/m²/week.	
Reporting group title	Etanercept Only
Reporting group description:	
Subjects received weekly subcutaneous injections of etanercept at a dose of 0.8 mg/kg.	

Serious adverse events	Methotrexate Only	Etanercept + Methotrexate	Etanercept Only
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 197 (7.11%)	28 / 294 (9.52%)	9 / 103 (8.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Raynaud's phenomenon			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Appendicectomy			

subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesicoureteral reflux surgery			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Immune system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 197 (1.02%)	0 / 294 (0.00%)	0 / 103 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Injury, poisoning and procedural complications			
Tibia fracture			

subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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			
Headache			
subjects affected / exposed	0 / 197 (0.00%)	3 / 294 (1.02%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Optic neuritis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
Photophobia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Ascites			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Constipation			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Nausea			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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

Oesophageal achalasia			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Oesophagitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Dermatomyositis			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perianal abscess			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Nephrotic syndrome			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Ureteric obstruction			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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

Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Hypothyroidism			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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			
subjects affected / exposed	1 / 197 (0.51%)	5 / 294 (1.70%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 197 (0.51%)	1 / 294 (0.34%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 197 (0.51%)	1 / 294 (0.34%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aseptic meningitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Bacteremia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Cellulitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Epstein-Barr virus infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Herpes zoster			

subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Infection			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Mycoplasma infection			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Pneumonia			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Sinusitis			
subjects affected / exposed	1 / 197 (0.51%)	0 / 294 (0.00%)	0 / 103 (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
Urinary tract infection			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Urosepsis			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Varicella			

subjects affected / exposed	1 / 197 (0.51%)	1 / 294 (0.34%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 197 (0.00%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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
Diabetes mellitus insulin-dependent			
subjects affected / exposed	0 / 197 (0.00%)	1 / 294 (0.34%)	0 / 103 (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

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Methotrexate Only	Etanercept + Methotrexate	Etanercept Only
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 197 (10.66%)	30 / 294 (10.20%)	10 / 103 (9.71%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 197 (3.05%)	1 / 294 (0.34%)	0 / 103 (0.00%)
occurrences (all)	8	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 197 (2.03%)	1 / 294 (0.34%)	0 / 103 (0.00%)
occurrences (all)	5	1	0
Hepatic enzyme increased			

subjects affected / exposed	4 / 197 (2.03%)	0 / 294 (0.00%)	0 / 103 (0.00%)
occurrences (all)	5	0	0
Injury, poisoning and procedural complications			
Treatment noncompliance			
subjects affected / exposed	0 / 197 (0.00%)	3 / 294 (1.02%)	0 / 103 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 197 (0.00%)	3 / 294 (1.02%)	1 / 103 (0.97%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 197 (0.51%)	4 / 294 (1.36%)	1 / 103 (0.97%)
occurrences (all)	1	5	1
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	2 / 197 (1.02%)	3 / 294 (1.02%)	2 / 103 (1.94%)
occurrences (all)	3	3	2
Agitation			
subjects affected / exposed	3 / 197 (1.52%)	0 / 294 (0.00%)	1 / 103 (0.97%)
occurrences (all)	4	0	1
Anger			
subjects affected / exposed	2 / 197 (1.02%)	0 / 294 (0.00%)	0 / 103 (0.00%)
occurrences (all)	3	0	0
Anxiety			
subjects affected / exposed	2 / 197 (1.02%)	3 / 294 (1.02%)	3 / 103 (2.91%)
occurrences (all)	3	3	5
Depression			
subjects affected / exposed	3 / 197 (1.52%)	11 / 294 (3.74%)	3 / 103 (2.91%)
occurrences (all)	3	12	3
Insomnia			
subjects affected / exposed	0 / 197 (0.00%)	3 / 294 (1.02%)	2 / 103 (1.94%)
occurrences (all)	0	3	2
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	2 / 197 (1.02%)	6 / 294 (2.04%)	0 / 103 (0.00%)
occurrences (all)	2	6	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 197 (0.00%)	3 / 294 (1.02%)	0 / 103 (0.00%)
occurrences (all)	0	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported