Clinical trial results:
A Multicenter, Randomized, Double-Dummy, Double-Blind Study Evaluating Two Doses of Adalimumab versus Methotrexate (MTX) in Pediatric Subjects with Chronic Plaque Psoriasis (Ps)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-013072-52
Trial protocol	DE BE ES CZ HU IT Outside EU/EEA NL
Global end of trial date	03 February 2015

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	M04-717

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01251614
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	David A Williams, AbbVie, david.a.williams@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000366-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	03 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to determine the safety and efficacy of 2 doses of adalimumab versus MTX in pediatric subjects with severe chronic plaque psoriasis, to determine the time to loss of disease control, the ability to regain response upon re-treatment, and to examine the pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration in this subject population.

Protection of trial subjects:

The investigator or his/her representative explained the nature of the study to the subject and the subject's parent/legal guardian, and answered all questions regarding this study. Paediatric subjects were included in all discussions in order to obtain verbal or written assent.
Prior to any study-related screening procedures being performed on the subject, the informed consent statement was reviewed and signed and dated by the subject's parent/legal guardian and the person who administered the informed consent, and any other signatories according to local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Canada: 28
Worldwide total number of subjects	114
EEA total number of subjects	69

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)	42
Adolescents (12-17 years)	61
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were to be children (from 4 to 11 years of age) and adolescents (from 12 through 17 years of age) with a clinical diagnosis of Ps for at least 6 months. Eligible subjects must have failed topical therapy and required systemic therapy to control their disease.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Methotrexate

Arm description:

Subjects received 0.1 mg/kg methotrexate at Baseline (Week 0), and up to 0.4 mg/kg weekly (maximum dose of 25 mg/week) in Period A. Subjects also received adalimumab placebo as a single subcutaneous loading dose at Week 0, followed by every other week (eow) dosing from Week 1.
Subjects who were non-responders in period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate 0.1 mg/kg at Week 0 and up to 0.4 mg/kg per week (maximum dose of 25 mg/week) orally.

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

Dosage and administration details:

A single SC loading dose at Week 0 followed by eow dosing beginning at Week 1.

Arm title	Adalimumab 0.4 mg/kg

Arm description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.4 mg/kg (up to a maximum of 20 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label

adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.4 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.4 mg/kg eow.

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

Dosage and administration details:

Adalimumab by subcutaneous injection every other week (EOW)

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

Dosage and administration details:

Orally once a week

Arm title	Adalimumab 0.8 mg/kg

Arm description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.8 mg/kg (up to a maximum of 40 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

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

Dosage and administration details:

Adalimumab by subcutaneous injection every other week (EOW)

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

Dosage and administration details:

Orally once a week

Number of subjects in period 1	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg
Started	37	39	38
Entered Period B	13 [1]	18 [2]	23 [3]
Entered Period C	8 [4]	11 [5]	19 [6]
Entered Period D	36	36	36
Completed	34	26	30
Not completed	3	13	8
Consent withdrawn by subject	-	2	1
Loss of disease control	-	1	-
Pregnancy	-	-	2
Adverse event	1	-	1
Lost to follow-up	-	1	-
Lack of efficacy	1	9	4
Almost total clearing of psoriatic lesions	1	-	-

Notes:

[1] - 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: Only subjects who were responders at Week 16 (Period A) entered the Treatment Withdrawal Phase (Period B)

[2] - 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: Only subjects who were responders at Week 16 (Period A) entered the Treatment Withdrawal Phase (Period B)

[3] - 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: Only subjects who were responders at Week 16 (Period A) entered the Treatment Withdrawal Phase (Period B)

[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: Only subjects who experienced loss of disease control in Period B entered the Re-Treatment Phase (Period C)

[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: Only subjects who experienced loss of disease control in Period B entered the Re-Treatment Phase (Period C)

[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: Only subjects who experienced loss of disease control in Period B entered the Re-Treatment Phase (Period C)

Baseline characteristics

Reporting groups	
Reporting group title	Methotrexate

Reporting group description:

Subjects received 0.1 mg/kg methotrexate at Baseline (Week 0), and up to 0.4 mg/kg weekly (maximum dose of 25 mg/week) in Period A. Subjects also received adalimumab placebo as a single subcutaneous loading dose at Week 0, followed by every other week (eow) dosing from Week 1.
Subjects who were non-responders in period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

Reporting group title	Adalimumab 0.4 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.4 mg/kg (up to a maximum of 20 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.4 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.4 mg/kg eow.

Reporting group title	Adalimumab 0.8 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.8 mg/kg (up to a maximum of 40 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

Reporting group values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg
Number of subjects	37	39	38
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	13.4	12.6	13
standard deviation	± 3.49	± 4.43	± 3.29

Gender categorical Units: Subjects			
Female	26	18	21
Male	11	21	17

Reporting group values	Total		
Number of subjects	114		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	65		
Male	49		

End points

End points reporting groups

Reporting group title	Methotrexate

Reporting group description:

Subjects received 0.1 mg/kg methotrexate at Baseline (Week 0), and up to 0.4 mg/kg weekly (maximum dose of 25 mg/week) in Period A. Subjects also received adalimumab placebo as a single subcutaneous loading dose at Week 0, followed by every other week (eow) dosing from Week 1.
Subjects who were non-responders in period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

Reporting group title	Adalimumab 0.4 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.4 mg/kg (up to a maximum of 20 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.4 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.4 mg/kg eow.

Reporting group title	Adalimumab 0.8 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.8 mg/kg (up to a maximum of 40 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.
Subjects who were non-responders in Period A entered Period D directly and received open-label adalimumab at 0.8 mg/kg eow for up to 52 weeks.
Subjects who responded in Period A entered the Treatment Withdrawal Phase (Period B) for up to 36 weeks. Subjects who experienced a loss of disease control in Period B entered the Re-treatment Phase (Period C) and received blinded adalimumab 0.8 mg/kg eow for 16 weeks. Subjects who completed Period B with no loss of disease control entered Period D and were observed off study medication for up to 52 weeks.
Subjects who completed Period C entered Period D for an additional 52 weeks of treatment with blinded adalimumab 0.8 mg/kg eow.

Primary: Percentage of Subjects Who Achieved a Psoriasis Area and Severity Index (PASI) 75 Response at Week 16

End point title	Percentage of Subjects Who Achieved a Psoriasis Area and Severity Index (PASI) 75 Response at Week 16

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-75 response is the percentage of participants who achieved at least a 75% reduction (improvement) from Baseline in PASI score at Week 16.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Primary

End point timeframe:
Baseline and Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)	32.4	43.6	57.9	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Methotrexate v Adalimumab 0.8 mg/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.027
Method	Chi-squared
Parameter estimate	Difference
Point estimate	-25.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.2
upper limit	-3.7

Notes:

[1] - The a priori defined order of the statistical hypotheses was as follows:
1. Superiority of adalimumab 0.8 mg/kg versus MTX, for the proportion of subjects achieving a ≥ PASI 75 response at Week 16.
2. Superiority of adalimumab 0.8 mg/kg versus MTX, for the proportion of subjects achieving a PGA cleared or minimal at Week 16.
This order was adhered to for confirmatory testing, all statistical tests were to be done at a level of significance of 5% and the overall type I error was preserved.

Primary: Percentage of Subjects Achieving a Physician's Global Assessment of Disease Activity (PGA) of "Cleared" or "Minimal" (0 or 1) at Week 16

End point title	Percentage of Subjects Achieving a Physician's Global Assessment of Disease Activity (PGA) of "Cleared" or "Minimal" (0 or 1) at Week 16

End point description:

The PGA is a 6-point scale used to measure the severity of disease at the time of the evaluation. The degree of overall lesion severity was evaluated using the following categories:
0: No evidence of scaling, erythema, or plaque elevation, overall score of cleared;
1: Occasional fine scale over <5% of lesions, faint erythema, minimal plaque elevation, overall score of minimal;
2: Fine scale dominates, light red coloration, mild plaque elevation, overall score of mild;
3: Course scale dominates, moderate red coloration, moderate plaque elevation, overall score of moderate;
4: Thick non-tenacious scale dominates, bright red coloration, marked plaque elevation, overall score of marked;
5: Very thick tenacious scale predominates, dusky to deep red coloration, severe plaque elevation,

overall score of severe.
The percentage of participants achieving a score of clear (0) or minimal (1) is reported. Non-responder imputation was used, the analysis was conducted in the ITT population.

End point type	Primary

End point timeframe:

Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)	40.5	41	60.5	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Methotrexate v Adalimumab 0.8 mg/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.083
Method	Chi-squared
Parameter estimate	Difference
Point estimate	-20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.2
upper limit	2.2

Notes:

[2] - The a priori defined order of the statistical hypotheses was as follows:
1. Superiority of adalimumab 0.8 mg/kg versus MTX, for the proportion of subjects achieving a ≥ PASI 75 response at Week 16.
2. Superiority of adalimumab 0.8 mg/kg versus MTX, for the proportion of subjects achieving a PGA cleared or minimal at Week 16.
This order was adhered to for confirmatory testing, all statistical tests were to be done at a level of significance of 5% and the overall type I error was preserved.

Secondary: Percentage of Subjects Who Achieved a PASI 90 Response at Week 16

End point title	Percentage of Subjects Who Achieved a PASI 90 Response at Week 16

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-90 response is the percentage of participants who achieved at least a 90% reduction (improvement) from Baseline in PASI score at Week 16.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)	21.6	30.8	28.9	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Adalimumab 0.8 mg/kg v Methotrexate
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.466
Method	Chi-squared
Parameter estimate	Difference
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.9
upper limit	12.3

Notes:

[3] - Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Secondary: Percentage of Subjects Who Achieved a PASI 100 Response at Week 16

End point title	Percentage of Subjects Who Achieved a PASI 100 Response at Week 16

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-100 response is the percentage of participants who achieved a 100% reduction (improvement) from Baseline in PASI score at Week 16.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)	2.7	10.3	18.4	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Adalimumab 0.8 mg/kg v Methotrexate
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.056
Method	Fisher exact
Parameter estimate	Difference
Point estimate	-15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	-2.3

Notes:

[4] - Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Secondary: Change From Baseline in the Children's Dermatology Life Quality Index (CDLQI) Scores at Week 16

End point title	Change From Baseline in the Children's Dermatology Life Quality Index (CDLQI) Scores at Week 16

End point description:

The Children's Dermatology Life Quality Index (CDLQI) is a 10-item questionnaire to measure the quality of life in children aged from 4 to 16 years.
Each question is scored from 0 (not at all) to 3 (very much). The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.
Last observation carried forward (LOCF) imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	38	38	
Units: units on a scale				
arithmetic mean (standard deviation)	-5 (± 7.11)	-4.9 (± 6.16)	-6.6 (± 6.22)	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Methotrexate v Adalimumab 0.8 mg/kg
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.304
Method	ANOVA
Parameter estimate	Difference
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	4.7

Notes:

[5] - Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Secondary: Change From Baseline in the Pediatric Quality of Life Inventory (PedsQL) Score at Week 16

End point title	Change From Baseline in the Pediatric Quality of Life Inventory (PedsQL) Score at Week 16

End point description:

The PedsQL Measurement Model measures health-related quality of life (HRQOL) in children and adolescents. The 23-item PedsQL Generic Core Scale includes Physical, Emotional, Social, School Functioning dimensions. Each item is scored from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL; the total score therefore ranges from 0 (worst) to 100 (best).
LOCF imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	38	38	
Units: units on a scale				
arithmetic mean (standard deviation)	1.9 (± 10.41)	9.5 (± 12.25)	10.8 (± 15.38)	

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX
Comparison groups	Adalimumab 0.8 mg/kg v Methotrexate
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.005
Method	ANOVA
Parameter estimate	Difference
Point estimate	-8.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.94
upper limit	-2.82

Notes:

[6] - Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Secondary: Percentage of Subjects Achieving a PGA of "Cleared" or "Minimal" (0 or 1) Upon Re-Treatment in Period C

End point title	Percentage of Subjects Achieving a PGA of "Cleared" or "Minimal" (0 or 1) Upon Re-Treatment in Period C

End point description:

The PGA is a 6-point scale used to measure the severity of disease at the time of the evaluation. The degree of overall lesion severity was evaluated using the following categories:
0: No evidence of scaling, erythema, or plaque elevation, overall score of cleared;
1: Occasional fine scale over <5% of lesions, faint erythema, minimal plaque elevation, overall score of minimal;
2: Fine scale dominates, light red coloration, mild plaque elevation, overall score of mild;
3: Course scale dominates, moderate red coloration, moderate plaque elevation, overall score of moderate;
4: Thick non-tenacious scale dominates, bright red coloration, marked plaque elevation, overall score of marked;
5: Very thick tenacious scale predominates, dusky to deep red coloration, severe plaque elevation, overall score of severe.
The percentage of participants achieving a score of clear (0) or minimal (1) is reported. Non-responder imputation was used, the analysis was conducted in the ITT population.

End point type	Secondary

End point timeframe:

Period C, Week 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8[7]	11[8]	19[9]	
Units: percentage of subjects				
number (not applicable)	62.5	27.3	52.6	

Notes:

[7] - Subjects in Period C

[8] - Subjects in Period C

[9] - Subjects in Period C

Statistical analyses

Statistical analysis title	Adalimumab 0.8mg/kg + MTX vs Adalimuimab 0.4 mg/kg

Statistical analysis description:

The difference between the combined adalimumab 0.8 mg/kg + MTX groups and the adalimumab 0.4 mg/kg group.

Comparison groups	Adalimumab 0.8 mg/kg v Adalimumab 0.4 mg/kg v Methotrexate
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.113
Method	Chi-squared
Parameter estimate	Difference
Point estimate	-28.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.6
upper limit	4

Notes:

[10] - Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Secondary: Time to Loss of Disease Control in Period B

End point title	Time to Loss of Disease Control in Period B

End point description:

Loss of disease control was defined as a worsening of PGA scores in comparison to Week 16 of Period A by at least 2 grades after treatment withdrawal. The PGA is a 6-point scale used to measure the severity of disease at the time of the evaluation. Scores range from 0 (no evidence of scaling, erythema, or plaque elevation) to 5 (very thick tenacious scale predominates, dusky to deep red coloration, severe plaque elevation).
This analysis was conducted in the ITT population, no imputation was used.

End point type	Secondary

End point timeframe:

Period B - 36 weeks

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13[11]	18[12]	23[13]	
Units: days				
median (inter-quartile range (Q1-Q3))	184 (84 to 335)	217 (56 to 551)	118 (79 to 194)	

Notes:

[11] - Subjects in Period B

[12] - Subjects in Period B

[13] - Subjects in Period B

Statistical analyses

Statistical analysis title	Adalimumab 0.8 mg/kg versus MTX

Statistical analysis description:

Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Comparison groups	Adalimumab 0.8 mg/kg v Methotrexate
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.17

Statistical analysis title	Adalimumab 0.8 mg/kg versus Adalimumab 0.4 mg/kg

Statistical analysis description:

Statistical comparisons for the ranked secondary endpoints were carried out in hierarchical order. All statistical tests were to be 2-sided with the significance level of 5%. Statistically significant results (P value ≤ 0.05) must have been achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank.

Comparison groups	Adalimumab 0.8 mg/kg v Adalimumab 0.4 mg/kg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	3.21

Secondary: Percentage of Subjects Achieving a PGA of "Cleared" or "Minimal" (0 or 1) Over Time

End point title	Percentage of Subjects Achieving a PGA of "Cleared" or "Minimal" (0 or 1) Over Time

End point description:

The PGA is a 6-point scale used to measure the severity of disease at the time of the evaluation. The degree of overall lesion severity was evaluated using the following categories:
0: No evidence of scaling, erythema, or plaque elevation, overall score of cleared;
1: Occasional fine scale over <5% of lesions, faint erythema, minimal plaque elevation, overall score of minimal;
2: Fine scale dominates, light red coloration, mild plaque elevation, overall score of mild;
3: Course scale dominates, moderate red coloration, moderate plaque elevation, overall score of moderate;
4: Thick non-tenacious scale dominates, bright red coloration, marked plaque elevation, overall score of marked;
5: Very thick tenacious scale predominates, dusky to deep red coloration, severe plaque elevation, overall score of severe.
The percentage of participants achieving a score of clear (0) or minimal (1) is reported. Non-responder imputation was used, the analysis was conducted in the ITT population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 11, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	8.1	20.5	28.9	
Period A, Week 8	8.1	35.9	44.7	
Period A, Week 11	18.9	30.8	47.4	
Period C, Week 0 (n=8, 11, 19)	0	0	0	
Period C, Week 16 (n=8, 11, 19)	62.5	27.3	52.6	
Period D, Week 0 (n=36, 36, 36)	30.6	19.4	38.9	
Period D, Week 16 (n=36, 36, 36)	77.8	38.9	50	
Period D, Week 28 (n=36, 36, 36)	69.4	50	63.9	
Period D, Week 40 (n=36, 36, 36)	69.4	50	61.1	
Period D, Week 52 (n=36, 36, 36)	75	50	55.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a PGA of "Cleared" (0) Over Time

End point title	Percentage of Subjects Achieving a PGA of "Cleared" (0) Over Time

End point description:

The PGA is a 6-point scale used to measure the severity of disease at the time of the evaluation. The degree of overall lesion severity was evaluated using the following categories:
0: No evidence of scaling, erythema, or plaque elevation, overall score of cleared;
1: Occasional fine scale over <5% of lesions, faint erythema, minimal plaque elevation, overall score of minimal;
2: Fine scale dominates, light red coloration, mild plaque elevation, overall score of mild;
3: Course scale dominates, moderate red coloration, moderate plaque elevation, overall score of moderate;
4: Thick non-tenacious scale dominates, bright red coloration, marked plaque elevation, overall score of marked;
5: Very thick tenacious scale predominates, dusky to deep red coloration, severe plaque elevation, overall score of severe.
The percentage of participants achieving a score of clear (0) is reported. Non-responder imputation was used, the analysis was conducted in the ITT population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 11, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	0	2.6	2.6	
Period A, Week 8	0	12.8	5.3	
Period A, Week 11	0	10.3	10.5	
Period C, Week 0 (n=8, 11, 19)	0	0	0	
Period C, Week 16 (n=8, 11, 19)	25	9.1	15.8	
Period D, Week 0 (n=36, 36, 36)	8.3	5.6	11.1	
Period D, Week 16 (n=36, 36, 36)	25	11.1	25	
Period D, Week 28 (n=36, 36, 36)	33.3	16.7	22.2	
Period D, Week 40 (n=36, 36, 36)	33.3	16.7	27.8	
Period D, Week 52 (n=36, 36, 36)	41.7	25	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved a PASI 50 Response Over Time

End point title	Percentage of Subjects Who Achieved a PASI 50 Response Over Time

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions

and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-50 response is the percentage of participants who achieved at least a 50% reduction (improvement) from Baseline in PASI score.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8, 11 and 16, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	16.2	41	52.6	
Period A, Week 8	40.5	56.4	65.8	
Period A, Week 11	51.4	61.5	71.1	
Period A, Week 16	54.1	66.7	78.9	
Period C, Week 0 (n=8, 11, 19)	62.5	90.9	52.6	
Period C, Week 16 (n=8, 11, 19)	87.5	90.9	89.5	
Period D, Week 0 (n=36, 36, 36)	52.8	63.9	75	
Period D, Week 16 (n=36, 36, 36)	91.7	69.4	88.9	
Period D, Week 28 (n=36, 36, 36)	88.9	72.2	86.1	
Period D, Week 40 (n=36, 36, 36)	91.7	63.9	83.3	
Period D, Week 52 (n=36, 36, 36)	91.7	66.7	77.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved a PASI 75 Response Over Time

End point title	Percentage of Subjects Who Achieved a PASI 75 Response Over Time

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-75 response is the percentage of participants who achieved at least a 75% reduction (improvement) from Baseline in PASI score.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 11, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	0	15.4	23.7	
Period A, Week 8	13.5	38.5	47.4	
Period A, Week 11	21.6	43.6	60.5	
Period C, Week 0 (n=8, 11, 19)	37.5	18.2	21.1	
Period C, Week 16 (n=8, 11, 19)	75	54.5	78.9	
Period D, Week 0 (n=36, 36, 36)	30.6	27.8	50	
Period D, Week 16 (n=36, 36, 36)	86.1	50	61.1	
Period D, Week 28 (n=36, 36, 36)	80.6	58.3	77.8	
Period D, Week 40 (n=36, 36, 36)	77.8	52.8	75	
Period D, Week 52 (n=36, 36, 36)	86.1	47.2	72.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved a PASI 90 Response Over Time

End point title	Percentage of Subjects Who Achieved a PASI 90 Response Over Time

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-90 response is the percentage of participants who achieved at least a 90% reduction (improvement) from Baseline in PASI score.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 11, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	0	5.1	5.3	
Period A, Week 8	2.7	20.5	23.7	
Period A, Week 11	2.7	28.2	28.9	
Period C, Week 0 (n=8, 11, 19)	0	0	10.5	
Period C, Week 16 (n=8, 11, 19)	62.5	27.3	57.9	
Period D, Week 0 (n=36, 36, 36)	25	16.7	36.1	
Period D, Week 16 (n=36, 36, 36)	63.9	36.1	38.9	
Period D, Week 28 (n=36, 36, 36)	55.6	33.3	41.7	

Period D, Week 40 (n=36, 36, 36)	55.6	36.1	47.2	
Period D, Week 52 (n=36, 36, 36)	66.7	33.3	44.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved a PASI 100 Response Over Time

End point title	Percentage of Subjects Who Achieved a PASI 100 Response Over Time

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis). A PASI-100 response is the percentage of participants who achieved a 100% reduction (improvement) from Baseline in PASI score.
Non-responder imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 11, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	0	0	2.6	
Period A, Week 8	0	5.1	5.3	
Period A, Week 11	0	5.1	10.5	
Period C, Week 0 (n=8, 11, 19)	0	0	0	
Period C, Week 16 (n=8, 11, 19)	25	9.1	15.8	
Period D, Week 0 (n=36, 36, 36)	8.3	5.6	11.1	
Period D, Week 16 (n=36, 36, 36)	13.9	11.1	25	
Period D, Week 28 (n=36, 36, 36)	27.8	13.9	19.4	
Period D, Week 40 (n=36, 36, 36)	30.6	13.9	22.2	
Period D, Week 52 (n=36, 36, 36)	41.7	25	22.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in PASI Score Over Time

End point title	Percent Change From Baseline in PASI Score Over Time

End point description:

PASI is a composite score based on the degree of effect on body surface area of psoriasis and the extension of erythema (reddening), induration (plaque thickness), desquamation (scaling) of the lesions and area affected as observed on the day of examination. The score ranges from 0 (no psoriasis) to 72 (very severe psoriasis).
LOCF imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline, Period A, Weeks 4, 8, 11 and 16, Period C, Weeks 0 and 16, Period D, Weeks 0, 16, 28, 40 and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percent change				
arithmetic mean (standard deviation)				
Period A, Week 4	-14 (± 36.71)	-36.9 (± 38.62)	-48.3 (± 33.96)	
Period A, Week 8	-30.6 (± 45.89)	-48.8 (± 44.74)	-60.3 (± 35.98)	
Period A, Week 11	-36.6 (± 51.69)	-51.4 (± 50.19)	-62.8 (± 38.02)	
Period A, Week 16	-42.8 (± 54.24)	-52.4 (± 51.79)	-65.6 (± 39.44)	
Period C, Week 0 (n=8, 11, 19)	-59 (± 20.61)	-65.3 (± 12.16)	-45.8 (± 39.64)	
Period C, Week 16 (n=8, 11, 19)	-87.1 (± 16.47)	-74.5 (± 17.79)	-69.3 (± 69.79)	
Period D, Week 0 (n=36, 36, 36)	-41.8 (± 54.99)	-46.8 (± 49.27)	-61.5 (± 42.96)	
Period D, Week 16 (n=36, 36, 36)	-82.3 (± 31.38)	-66.9 (± 33.51)	-74.5 (± 37.44)	
Period D, Week 28 (n=36, 36, 36)	-81 (± 35.86)	-65.8 (± 36.99)	-81.5 (± 22.06)	
Period D, Week 40 (n=36, 36, 36)	-83 (± 31.94)	-64.6 (± 37.46)	-82.1 (± 23.99)	
Period D, Week 52 (n=36, 36, 36)	-86.3 (± 28.92)	-58.7 (± 53.21)	-80.1 (± 24.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CDLQI Over Time

End point title	Change From Baseline in CDLQI Over Time

End point description:

The Children's Dermatology Life Quality Index (CDLQI) is a 10-item questionnaire to measure the quality of life in children aged from 4 to 16 years.
Each question is scored from 0 (not at all) to 3 (very much). The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

LOCF imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline, Period A, Weeks 4, and 8 , Period C, Weeks 0 and 4, Period D, Weeks 0, 11, 28, and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	38	38	
Units: units on a scale				
arithmetic mean (standard deviation)				
Period A, Week 4	-2.9 (± 5.24)	-3.9 (± 5.22)	-4.9 (± 5.8)	
Period A, Week 8	-4 (± 6.44)	-4.1 (± 6.29)	-5.5 (± 5.66)	
Period C, Week 0 (n=8, 11, 19)	-6.1 (± 4.55)	-4.7 (± 9.08)	-6.1 (± 6.92)	
Period C, Week 4 (n=8, 11, 19)	-9.8 (± 3.92)	-5.5 (± 7.24)	-7 (± 6.63)	
Period D, Week 0 (n=35, 35, 36)	-5.6 (± 7.55)	-5.5 (± 5.95)	-6.8 (± 6.7)	
Period D, Week 11 (n=35, 35, 36)	-8.5 (± 5.37)	-6.8 (± 7.07)	-7.4 (± 6.21)	
Period D, Week 28 (n=35, 35, 36)	-8.3 (± 5.93)	-6.8 (± 7.91)	-8.4 (± 6.72)	
Period D, Week 52 (n=35, 35, 36)	-8.4 (± 6.08)	-6.6 (± 8.12)	-8.2 (± 6.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With CDLQI = 0 Over Time

End point title	Percentage of Subjects With CDLQI = 0 Over Time

End point description:

The Children's Dermatology Life Quality Index (CDLQI) is a 10-item questionnaire to measure the quality of life in children aged from 4 to 16 years.
Each question is scored from 0 (not at all) to 3 (very much). The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired and a score of 0 indicates no impairment in quality of life.
Non-responder imputation was used, the analysis was conducted in the intent to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8 and 16 , Period C, Weeks 0 and 4, Period D, Weeks 0, 11, 28, and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: percentage of subjects				
number (not applicable)				
Period A, Week 4	5.4	5.1	10.5	
Period A, Week 8	10.8	12.8	5.3	

Period A, Week 16	10.8	20.5	23.7	
Period C, Week 0 (n=8, 11, 19)	0	36.4	21.1	
Period C, Week 4 (n=8, 11, 19)	12.5	36.4	31.6	
Period D, Week 0 (n=36, 36, 36)	16.7	22.2	27.8	
Period D, Week 11 (n=36, 36, 36)	25	16.7	33.3	
Period D, Week 28 (n=36, 36, 36)	30.6	22.2	30.6	
Period D, Week 52 (n=36, 36, 36)	41.7	16.7	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PASI 50/75/90/100 Response in Period A

End point title	Time to PASI 50/75/90/100 Response in Period A

End point description:

Subjects who did not have a response during Period A were censored. "99999" indicates parameters that were not estimable.

End point type	Secondary

End point timeframe:

Period A, 16 weeks

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	38	
Units: days				
median (inter-quartile range (Q1-Q3))				
PASI 50	76 (56 to 112)	55 (28 to 115)	30 (28 to 77)	
PASI 75	116 (111 to 99999)	107 (56 to 99999)	59 (53 to 99999)	
PASI 90	99999 (112 to 99999)	99999 (78 to 99999)	99999 (76 to 99999)	
PASI 100	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PedsQL Over Time

End point title	Change From Baseline in PedsQL Over Time

End point description:

The PedsQL Measurement Model measures health-related quality of life (HRQOL) in children and adolescents. The 23-item PedsQL Generic Core Scale includes Physical, Emotional, Social, School Functioning dimensions. Each item is scored from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale, so that higher scores indicate better HRQOL; the total

score therefore ranges from 0 (worst) to 100 (best).
LOCF imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Baseline, Period A, Weeks 4 and 8 , Period C, Weeks 0 and 4, Period D, Weeks 0, 11, 28, and 52

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	38	38	
Units: units on a scale				
arithmetic mean (standard deviation)				
Period A, Week 4 (n=37, 38, 36)	-0.8 (± 11.75)	4.9 (± 13.8)	8.1 (± 11.95)	
Period A, Week 8 (n=37, 38, 38)	0.5 (± 10.18)	7 (± 13.16)	8.8 (± 15.45)	
Period C, Week 0 (n=8, 11, 19)	3 (± 10.45)	8.9 (± 25.35)	14.2 (± 20.25)	
Period C, Week 4 (n=8, 11, 19)	5.2 (± 11.08)	11.6 (± 25.19)	16.3 (± 17.35)	
Period D, Week 0 (n=36, 36, 36)	2.3 (± 10.93)	9.4 (± 16.9)	10.5 (± 15.86)	
Period D, Week 11 (n=36, 36, 36)	5.4 (± 10.36)	12.8 (± 19.03)	12 (± 16.13)	
Period D, Week 28 (n=36, 36, 36)	8 (± 13.4)	14.5 (± 20.19)	13.1 (± 16.23)	
Period D, Week 52 (n=36, 36, 36)	8.6 (± 13.93)	14 (± 20.4)	13.8 (± 15.36)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Children's Depression Inventory: Short (CDI:S)

End point title	Change From Baseline in the Children's Depression Inventory: Short (CDI:S)

End point description:

The CDI:S is a short 10-item self-rated symptom-oriented scale used to screen for depressive symptoms. CDI:S scores range from 0 to 100, with a lower score indicating fewer depressive symptoms.
LOCF imputation was used, the analysis was conducted in the intent-to-treat (ITT) population.

End point type	Secondary

End point timeframe:

Period A, Weeks 4, 8, and 16

End point values	Methotrexate	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	35	
Units: units on a scale				
arithmetic mean (standard deviation)				
Period A, Week 4 (n=35, 35, 34)	0.6 (± 8.85)	-1 (± 6.64)	-3.6 (± 5.86)	
Period A, Week 8 (n=35, 35, 34)	0.2 (± 5.26)	-1.5 (± 7.52)	-1.6 (± 5.52)	
Period A, Week 16 (n=35, 35, 35)	-2 (± 5.88)	-3.3 (± 8.12)	-2.3 (± 6.29)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period A - up to 16 weeks
Period B - up to 36 weeks
Period C - up to 16 weeks
Period D - up to 52 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Period A: Methotrexate

Reporting group description:

Subjects received 0.1 mg/kg methotrexate at Baseline (Week 0), and up to 0.4 mg/kg weekly (maximum dose of 25 mg/week) in Period A. Subjects also received adalimumab placebo as a single subcutaneous loading dose at Week 0, followed by every other week dosing from Week 1.

Reporting group title	Period A: Adalimumab 0.4 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab (ADA) 0.4 mg/kg (up to a maximum of 20 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.

Reporting group title	Period A: Adalimumab 0.8 mg/kg

Reporting group description:

In Period A subjects received a single subcutaneous loading dose of adalimumab 0.8 mg/kg (up to a maximum of 40 mg) at Week 0 followed by every other week dosing beginning at Week 1. To maintain the blind, subjects also received weekly dosing of methotrexate placebo tablets.

Reporting group title	Period B: MTX/No Treatment

Reporting group description:

Subjects initially randomized to methotrexate who responded in Period A were withdrawn from active therapy in Period B for up to 36 weeks.

Reporting group title	Period B: ADA 0.4 mg/kg/No Treatment

Reporting group description:

Subjects initially randomized to adalimumab (ADA) 0.4 mg/kg who responded in Period A were withdrawn from active therapy in Period B for up to 36 weeks.

Reporting group title	Period B: ADA 0.8 mg/kg/No Treatment

Reporting group description:

Subjects initially randomized to adalimumab (ADA) 0.8 mg/kg who responded in Period A were withdrawn from active therapy in Period B for up to 36 weeks.

Reporting group title	Period C: Adalimumab 0.4 mg/kg

Reporting group description:

Subjects initially randomized to adalimumab 0.4 mg/kg with loss of disease control in Period B received adalimumab 0.4 mg/kg eow for up to 16 weeks in Period C.

Reporting group title	Period C: Adalimumab 0.8 mg/kg

Reporting group description:

Subjects initially randomized to either methotrexate or adalimumab 0.8 mg/kg with loss of disease control in Period B received adalimumab 0.8 mg/kg eow for up to 16 weeks in Period C.

Reporting group title	Period D: Adalimumab 0.4 mg/kg

Reporting group description:

Subjects received adalimumab 0.4 mg/kg eow for up to 52 weeks in Period D.

Reporting group title	Period D: Adalimumab 0.8 mg/kg

Reporting group description:

Subjects received adalimumab 0.8 mg/kg eow for up to 52 weeks in Period D.

Serious adverse events	Period A: Methotrexate	Period A: Adalimumab 0.4 mg/kg	Period A: Adalimumab 0.8 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	3 / 39 (7.69%)	0 / 38 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eye Naevus			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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			
Fall			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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
Hand Fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	0 / 38 (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
Tendon Injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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
Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			

subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (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			
Agitation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	0 / 38 (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
Infections and infestations			
Gastrointestinal Infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	0 / 38 (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

Serious adverse events	Period B: MTX/No Treatment	Period B: ADA 0.4 mg/kg/No Treatment	Period B: ADA 0.8 mg/kg/No Treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eye Naevus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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			
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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

Hand Fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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
Tendon Injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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
Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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			
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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
Infections and infestations			
Gastrointestinal Infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (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	Period C:	Period C:	Period D:

	Adalimumab 0.4 mg/kg	Adalimumab 0.8 mg/kg	Adalimumab 0.4 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eye Naevus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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			
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
Hand Fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
Tendon Injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
Skin and subcutaneous tissue disorders			

Rash Maculo-Papular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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			
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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
Infections and infestations			
Gastrointestinal Infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (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	Period D: Adalimumab 0.8 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 87 (5.75%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Eye Naevus			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hand Fracture			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Tendon Injury			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Haemorrhagic Ovarian Cyst			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash Maculo-Papular			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastrointestinal Infection			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Period A: Methotrexate	Period A: Adalimumab 0.4 mg/kg	Period A: Adalimumab 0.8 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 37 (62.16%)	27 / 39 (69.23%)	23 / 38 (60.53%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Joint Injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Thermal Burn			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 37 (10.81%)	7 / 39 (17.95%)	6 / 38 (15.79%)
occurrences (all)	8	11	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	2 / 39 (5.13%)	0 / 38 (0.00%)
occurrences (all)	1	2	0
Chest Pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	2 / 37 (5.41%)	4 / 39 (10.26%)	0 / 38 (0.00%)
occurrences (all)	2	4	0
Injection Site Pain			

subjects affected / exposed	3 / 37 (8.11%)	1 / 39 (2.56%)	3 / 38 (7.89%)
occurrences (all)	3	1	3
Injection Site Reaction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	2 / 38 (5.26%)
occurrences (all)	0	1	2
Pyrexia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 39 (7.69%)	1 / 38 (2.63%)
occurrences (all)	1	3	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 37 (10.81%)	1 / 39 (2.56%)	1 / 38 (2.63%)
occurrences (all)	4	1	1
Abdominal Pain Upper			
subjects affected / exposed	0 / 37 (0.00%)	2 / 39 (5.13%)	1 / 38 (2.63%)
occurrences (all)	0	5	1
Diarrhoea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	0 / 38 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 39 (5.13%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	4 / 37 (10.81%)	3 / 39 (7.69%)	2 / 38 (5.26%)
occurrences (all)	5	3	2
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	3 / 39 (7.69%)	1 / 38 (2.63%)
occurrences (all)	0	3	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 37 (2.70%)	4 / 39 (10.26%)	1 / 38 (2.63%)
occurrences (all)	1	4	1
Dyspnoea			

subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal Pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 39 (2.56%)	2 / 38 (5.26%)
occurrences (all)	2	1	2
Rhinorrhoea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	3 / 38 (7.89%)
occurrences (all)	1	0	3
Eczema			
subjects affected / exposed	0 / 37 (0.00%)	2 / 39 (5.13%)	1 / 38 (2.63%)
occurrences (all)	0	2	1
Eczema Vesicular			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 37 (2.70%)	3 / 39 (7.69%)	1 / 38 (2.63%)
occurrences (all)	1	3	1
Pruritus Generalised			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 39 (2.56%)	1 / 38 (2.63%)
occurrences (all)	1	1	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Insomnia			

subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 39 (2.56%)	1 / 38 (2.63%)
occurrences (all)	2	1	1
Back Pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 39 (2.56%)	2 / 38 (5.26%)
occurrences (all)	0	2	2
Joint Effusion			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	3 / 37 (8.11%)	0 / 39 (0.00%)	2 / 38 (5.26%)
occurrences (all)	3	0	2
Influenza			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Lice Infestation			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	7 / 37 (18.92%)	10 / 39 (25.64%)	8 / 38 (21.05%)
occurrences (all)	9	11	10
Oral Herpes			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	1 / 38 (2.63%)
occurrences (all)	1	0	1
Pharyngitis			

subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	1	0	0
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 39 (2.56%)	3 / 38 (7.89%)
occurrences (all)	1	1	3
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 37 (16.22%)	4 / 39 (10.26%)	2 / 38 (5.26%)
occurrences (all)	8	4	2
Urinary Tract Infection			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 37 (0.00%)	0 / 39 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 37 (2.70%)	1 / 39 (2.56%)	1 / 38 (2.63%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 37 (2.70%)	1 / 39 (2.56%)	0 / 38 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Period B: MTX/No Treatment	Period B: ADA 0.4 mg/kg/No Treatment	Period B: ADA 0.8 mg/kg/No Treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	6 / 18 (33.33%)	6 / 23 (26.09%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Joint Injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Thermal Burn			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	2 / 18 (11.11%)	1 / 23 (4.35%)
occurrences (all)	1	2	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Chest Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injection Site Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injection Site Reaction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 13 (0.00%)	2 / 18 (11.11%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			

subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Eczema Vesicular			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pruritus Generalised			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Back Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Joint Effusion			

subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal Pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lice Infestation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 18 (5.56%)	4 / 23 (17.39%)
occurrences (all)	0	1	4
Oral Herpes			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 18 (11.11%)	1 / 23 (4.35%)
occurrences (all)	0	3	1

Urinary Tract Infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 13 (0.00%)	0 / 18 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Period C: Adalimumab 0.4 mg/kg	Period C: Adalimumab 0.8 mg/kg	Period D: Adalimumab 0.4 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	16 / 27 (59.26%)	8 / 13 (61.54%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Joint Injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Thermal Burn			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 11 (0.00%)	3 / 27 (11.11%)	1 / 13 (7.69%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Chest Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Injection Site Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Injection Site Reaction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abdominal Pain Upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			

subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	2 / 11 (18.18%)	1 / 27 (3.70%)	1 / 13 (7.69%)
occurrences (all)	2	1	1
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eczema Vesicular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	1 / 11 (9.09%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Pruritus Generalised			
subjects affected / exposed	1 / 11 (9.09%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Psoriasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	0 / 11 (0.00%)	3 / 27 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Joint Effusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal Pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Influenza			

subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Lice Infestation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	5 / 27 (18.52%)	3 / 13 (23.08%)
occurrences (all)	1	5	3
Oral Herpes			
subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 11 (0.00%)	3 / 27 (11.11%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Urinary Tract Infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 27 (3.70%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	0 / 11 (0.00%)	0 / 27 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 27 (7.41%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased Appetite			

subjects affected / exposed	1 / 11 (9.09%)	0 / 27 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Period D: Adalimumab 0.8 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 87 (73.56%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	3		
Joint Injury			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Thermal Burn			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 87 (25.29%)		
occurrences (all)	30		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Chest Pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Injection Site Pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Injection Site Reaction			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Abdominal Pain Upper			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	10 / 87 (11.49%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Cough			

subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	4		
Oropharyngeal Pain			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	7		
Rhinorrhoea			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	7		
Eczema Vesicular			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Pruritus Generalised			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	6		
Psychiatric disorders			
Agitation			

subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	4		
Back Pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	2		
Joint Effusion			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Musculoskeletal Pain			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 87 (5.75%)		
occurrences (all)	6		
Gastroenteritis			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	9 / 87 (10.34%)		
occurrences (all)	10		
Lice Infestation			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	25 / 87 (28.74%)		
occurrences (all)	36		
Oral Herpes			

subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	8		
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	3		
Upper Respiratory Tract Infection			
subjects affected / exposed	13 / 87 (14.94%)		
occurrences (all)	17		
Urinary Tract Infection			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2008	• added explanation for even-week dosing for Period D. • updated adalimumab worldwide approval status for Rheumatoid Arthritis. • updated Overall Study Design and Plan: minimum screening period changed from 48 to 72 hours, added information for the non-investigational medicinal product folic acid, added that subjects must complete all 16 weeks of treatment in Period C in order to be eligible to enter Period D. • Study activities updated to remove the Family Dermatology Quality of Life Index (FDLQI), added the Children's Depression Index:Short (CDI:S) at Week 4A and 8A visits and removed all patient reported outcomes (PROs) from Week 11A visit, general labs and urinalysis were added at Weeks 0D and 52D; pharmacokinetic (PK)/Anti-adalimumab antibody (AAA) sample collection was added at Week 8D. • Study procedures updated: language added regarding tuberculosis screening, lab analyses, FDLQI removed, CDLQI cartoon version removed, PedsQL parent proxy report for children ages 5-7 removed, information added for folic acid. • Drug Concentration Measurements: removed sample collection at Week 16C and added sample collection at Week 8D. • Secondary Variable, Ranked – Removed FDLQI • Treatments Administered: Information for MTX was added, adalimumab dosing schedules for Periods A, C, and D were added and Information for folic acid was added.
15 March 2011	• Update the date related to the number of countries that adalimumab has been approved • Add information on the maximum time subject would be participating in the study • Added Differences Statement. • Update inclusion criterion number 10 to include the QuantiFERON-TB Gold or equivalent test. • Add new inclusion criterion number 16 regarding updated immunization schedule. • Add wording on clinically significant abnormal screening laboratory results to exclusion criterion number 20. • Provide new information on Hepatitis B testing for exclusion criterion number 14. • Add new exclusion criterion number 23 regarding viral infections, and to incorporate adalimumab 0.8 mg/kg protocol wording. • Add new exclusion criterion number 24 related to GFR. • Add new exclusion criterion number 25 related to Hepatitis C. • Add additional prohibited medications. • Add general labs (hematology and chemistry) to the Week 8A visit Study Activities (Period A). • Add additional time point for assessment of hs-CRP to Study Activities (Period D). • Update chest x-ray and TB screening sections to include new information on QuantiFERON-TB Gold or equivalent test and to add content to include new adalimumab protocol standard wording. Add clarification that subjects enrolled under TB prophylaxis must continue the prophylaxis until entire course was completed. • Add instruction for measurement of waist circumference at level of umbilicus for metabolic syndrome screening and reference to WHO Child Growth Charts. • Add instructions on which version of PedsQL to complete as child ages during study. • Add guidance on scheduling annual TB testing.

18 July 2013	• Updated Adalimumab Overview to reflect current information, as provided in the updated Investigator's Brochure version 19. • Added Safety Information: section added to include new safety monitoring information. • Updated Prior and Concomitant Therapy: added collection requirements for events of malignancy in patients 30 years of age or younger. • Updated Prohibited Medications with newly available biologic therapies that are prohibited while in the study. • Updated the following sections to comply with the Humira® standard protocol language in compliance with Investigator's Brochure version 19 (dated May 2013) and AbbVie policies and procedures: - Discontinuation of Individual Subjects: added that noncompliance with TB prophylaxis was grounds for discontinuation; removed the language regarding inclusion/exclusion criteria where safety was involved, as violations of inclusion and/or exclusion criteria are not necessarily grounds for discontinuation and are handled by the study designated physician; for protocol consistency changed medical monitor to study designated physician. - Drug Accountability: differentiated between the refrigerated and nonrefrigerated study drug; clarification made to differentiated drug dispensing depot from drug destruction depot. - Protocol Deviations: statement added that AbbVie does not grant waivers or allow any known or prospective protocol deviations. • Adverse Event Reporting: added new requirements for reporting any serious adverse event or nonserious event of malignancy in patients 30 years of age or younger.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported