Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-Controlled Study of the Safety, Efficacy, and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Rheumatoid Arthritis

Summary

EudraCT number	2011-001661-40
Trial protocol	Outside EU/EEA
Global end of trial date	02 June 2010

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	07 June 2015

Trial information

Trial identification

Sponsor protocol code	DE038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00048542
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	Aileen L. Pangan MD , AbbVie, aileen.pangan@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000036-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	02 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a multicenter, Phase 3 randomized, placebo-controlled study designed to evaluate adalimumab in children 4 to 17 years old with polyarticular juvenile idiopathic arthritis (JIA) who are either methotrexate (MTX) treated or non-MTX treated.

Protection of trial subjects:

The subject and/or parent or legal guardian read and understood information provided about the study and signed an informed consent form. Additionally, a written informed assent was obtained from all children in accordance with individual IRB recommendations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2002
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	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 88
Worldwide total number of subjects	171
EEA total number of subjects	83

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	0

months)	
Children (2-11 years)	88
Adolescents (12-17 years)	82
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects enrolled at 31 sites in Belgium, Czech Republic, France, Germany, Italy,Slovakia, Spain, and the United States. Subjects were methotrexate (MTX)-naive or had been withdrawn from MTX at least 2 weeks prior to study drug administration (non-MTX stratum), or were inadequate responders to MTX and continued MTX treatment (MTX stratum).

Pre-assignment

Screening details:

A total of 171 subjects entered the Open-Label Lead-In (OL-LI) phase and received adalimumab; 160 subjects completed the OL-LI phase; and 133 entered the 32-week Double-Blind Phase (75 in the MTX stratum; 58 in the non-MTX stratum) and were randomized to adalimumab or placebo. For all groups, started indicates when subjects entered the DB Phase.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Adalimumab + MTX

Arm description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Arm type	Experimental
Investigational medicinal product name	Double-Blind Adalimumab/Placebo + MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 24 mg adalimumab or placebo per square meter of body surface area (BSA) every other week (eow) concomitantly with MTX treatment for 32 weeks during the Double-Blind phase. Total body dose of adalimumab was not to exceed 40 mg.

Arm title	Double-Blind Placebo + MTX

Arm description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Arm type	Placebo

Investigational medicinal product name	Double-Blind Adalimumab/Placebo + MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 24 mg adalimumab or placebo per square meter of body surface area (BSA) every other week (eow) concomitantly with MTX treatment for 32 weeks during the Double-Blind phase. Total body dose of adalimumab was not to exceed 40 mg.

Arm title	Double-Blind Adalimumab

Arm description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Arm type	Experimental
Investigational medicinal product name	Double-Blind Adalimumab/Placebo
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 24 mg adalimumab or placebo per square meter of body surface area (BSA) every other week (eow) without MTX treatment for 32 weeks during the Double-Blind Phase. Total body dose of adalimumab was not to exceed 40 mg.

Arm title	Double-Blind Placebo

Arm description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose, administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Arm type	Placebo
Investigational medicinal product name	Double-Blind Adalimumab/Placebo
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 24 mg adalimumab or placebo per square meter of body surface area (BSA) every other week (eow) without MTX treatment for 32 weeks during the Double-Blind Phase. Total body dose of adalimumab was not to exceed 40 mg.

Number of subjects in period 1[1]	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX	Double-Blind Adalimumab
Started	38	37	30
Completed	35	36	29
Not completed	3	1	1
Randomized in error	1	-	-
Consent withdrawn by subject	-	1	-

Sponsor request or decision	2	-	-
Protocol deviation	-	-	1

Number of subjects in period 1[1]	Double-Blind Placebo
Started	28
Completed	28
Not completed	0
Randomized in error	-
Consent withdrawn by subject	-
Sponsor request or decision	-
Protocol deviation	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: For all groups, started indicates when the subjects entered the DB Phase.

Period 2

Period 2 title	Open-label Extension BSA Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-label Extension BSA Adalimumab + MTX

Arm description:

Subjects in the methotrexate (MTX) stratum received subcutaneous injections of 24 mg adalimumab per square meter of body surface area (BSA) up to a maximum of 40 mg total body dose every other week (eow) concomitantly with MTX treatment during the Open-Label Extension BSA Phase of the study.

Arm type	Experimental
Investigational medicinal product name	OLE BSA Adalimumab/Placebo +/- MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Comparison of subcutaneous injection of 24 mg adalimumab per square meter of body surface area (BSA) every other week (eow) either with or without concomitant MTX treatment for a minimum of 44 weeks (up to a maximum of 136 weeks) during the Open-Label Extension BSA Phase.

Arm title	Open-label Extension BSA Adalimumab

Arm description:

Subjects in the non-methotrexate (MTX) stratum received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose SC eow) without concomitant MTX treatment during the Open-Label Extension BSA Phase.

Arm type	Experimental
Investigational medicinal product name	OLE BSA Adalimumab/Placebo +/- MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Comparison of subcutaneous injection of 24 mg adalimumab per square meter of body surface area (BSA) every other week (eow) either with or without concomitant MTX treatment for a minimum of 44 weeks (up to a maximum of 136 weeks) during the Open-Label Extension BSA Phase.

Number of subjects in period 2	Open-label Extension BSA Adalimumab + MTX	Open-label Extension BSA Adalimumab
Started	71	57
Completed	59	47
Not completed	12	10
Consent withdrawn by subject	3	6
Sponsor request or decision	5	1
Adverse event	1	1
Lack of efficacy	3	1
Protocol deviation	-	1

Period 3

Period 3 title	Open-label Extension Fixed Dose Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-label Extension FD Adalimumab + MTX

Arm description:

Subjects in the methotrexate (MTX) stratum received adalimumab concomitantly with MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study in which only body weight (not BSA) determined dosing. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Arm type	Experimental
Investigational medicinal product name	OLE FD Adalimumab/Placebo +/- MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Comparison of adalimumab administered subcutaneously every other week (eow) either with or without concomitant MTX treatment for up to 224 weeks during the Open-Label Extension Fixed Dose (FD) Phase.

Arm title	Open-label Extension FD Adalimumab

Arm description:

Subjects in the non-methotrexate (MTX) stratum received adalimumab without concomitant MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study in which body weight (not BSA) determined dosing. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Arm type	Experimental
Investigational medicinal product name	OLE FD Adalimumab/Placebo +/- MTX
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Comparison of adalimumab administered subcutaneously every other week (eow) either with or without concomitant MTX treatment for up to 224 weeks during the Open-Label Extension Fixed Dose (FD) Phase.

Number of subjects in period 3	Open-label Extension FD Adalimumab + MTX	Open-label Extension FD Adalimumab
Started	59	47
Completed	37	25
Not completed	22	22
Consent withdrawn by subject	6	3
Sponsor request or decision	6	7
Adverse event	2	2
Lost to follow-up	5	8
Protocol deviation	1	1
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Adalimumab + MTX
Reporting group description:	
Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.	
Reporting group title	Double-Blind Placebo + MTX
Reporting group description:	
Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.	
Reporting group title	Double-Blind Adalimumab
Reporting group description:	
Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.	
Reporting group title	Double-Blind Placebo
Reporting group description:	
Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose, administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.	

Reporting group values	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX	Double-Blind Adalimumab
Number of subjects	38	37	30
Age categorical Units: Subjects			
Age continuous			
Age for subjects in the Double-blind Phase only.			
Units: years arithmetic mean standard deviation	 11.7 ± 3.29	 10.8 ± 3.36	 11.1 ± 4.13
Gender categorical			
Numbers represent subjects in the Double-blind Phase only.			
Units: Subjects			
Female	30	30	23
Male	8	7	7

Reporting group values	Double-Blind Placebo	Total	
Number of subjects	28	133	

Age categorical Units: Subjects			

Age continuous			
Age for subjects in the Double-blind Phase only.			
Units: years			
arithmetic mean	11.3		
standard deviation	± 3.77	-	
Gender categorical			
Numbers represent subjects in the Double-blind Phase only.			
Units: Subjects			
Female	20	103	
Male	8	30	

End points

End points reporting groups

Reporting group title	Double-Blind Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Reporting group title	Double-Blind Placebo + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Reporting group title	Double-Blind Adalimumab

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Reporting group title	Double-Blind Placebo

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose, administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Reporting group title	Open-label Extension BSA Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum received subcutaneous injections of 24 mg adalimumab per square meter of body surface area (BSA) up to a maximum of 40 mg total body dose every other week (eow) concomitantly with MTX treatment during the Open-Label Extension BSA Phase of the study.

Reporting group title	Open-label Extension BSA Adalimumab

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose SC eow) without concomitant MTX treatment during the Open-Label Extension BSA Phase.

Reporting group title	Open-label Extension FD Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum received adalimumab concomitantly with MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study in which only body weight (not BSA) determined dosing. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Reporting group title	Open-label Extension FD Adalimumab

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum received adalimumab without concomitant MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study in which body weight (not BSA) determined dosing. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Subject analysis set title	Open-label Adalimumab + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received methotrexate (MTX) plus open-label adalimumab (24 mg/square meter up to a maximum of 40 mg total body dose by body surface area [BSA] administered subcutaneously [SC] every other week [eow]) during the Open-Label Lead-In (OL-LI) Phase of the study. The intent-to-treat (ITT) population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Open-label Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received open-label adalimumab (24 mg/square meter up to a maximum of 40 mg total body dose by body surface area [BSA] administered subcutaneously [SC] every other week [eow]), but no methotrexate (MTX), during the Open-Label Lead-In (OL-LI) Phase of the study. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab during the open-label lead-in phase and during the double-blind phase. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab during the open-label lead-in phase and placebo during the double-blind phase. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Adalimumab + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab plus MTX during the open-label lead-in phase and adalimumab plus MTX during the double-blind phase. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Placebo + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab plus MTX during the open-label lead-in phase and placebo plus MTX during the double-blind phase. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	OLE BSA Adalimumab + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab and concomitant MTX during the Open-Label Extension body surface area (BSA) phase. Subjects received OL adalimumab (24 mg/m2 BSA up to a maximum of 40 mg total body dose subcutaneously (SC) every other week (eow). The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	OLE BSA Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab, but not concomitant MTX, during the Open-Label Extension body surface area (BSA) phase. Subjects received OL adalimumab (24 mg/m2 BSA up to a maximum of 40 mg total body dose subcutaneously (SC) every other week (eow). The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	OLE FD Adalimumab + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab and concomitant MTX during the Open-Label Extension fixed dose phase. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab subcutaneously (SC) every other week (eow). Subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow. The ITT population was defined as all subjects who were randomized and who received at least a single

administration of study drug.

Subject analysis set title	OLE FD Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received adalimumab, but not concomitant MTX, during the Open-Label Extension Fixed Dose phase. Subjects weighing less than 30 kg were dosed with 20 mg of adalimumab subcutaneously (SC) every other week (eow). Subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Double-Blind Adalimumab + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Double-Blind Placebo + MTX
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Double-Blind Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study. The ITT population was defined as all subjects who were randomized and who received at least a single administration of study drug.

Subject analysis set title	Double-Blind Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose, administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Primary: Number of Subjects in the Non-MTX Stratum With Disease Flare During the Double-Blind Phase

End point title	Number of Subjects in the Non-MTX Stratum With Disease Flare During the Double-Blind Phase

End point description:

The primary efficacy endpoint was the number of adalimumab-treated subjects in the non-MTX stratum with disease flare during the Double-Blind Phase compared with the number of placebo-treated subjects in the non-MTX stratum with disease flare during the double-blind phase. Subjects met the criteria for disease flare if they had 1) >= 30% worsening in at least 3 of the 6 Juvenile Rheumatoid Arthritis (JRA) core set criteria and a minimum of 2 active joints, and 2) >= 30% improvement in not more than 1 of the 6 JRA core set criteria. Missing values were treated as disease flare.

End point type	Primary

End point timeframe:

Week 16 to Week 48 (32 weeks)

End point values	Double-Blind Adalimumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[1]	28[2]		
Units: subjects	13	20		

Notes:

[1] - All subjects in the ITT population in the non-MTX stratum.

[2] - All subjects in the ITT population in the non-MTX stratum.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The study was sized to detect a difference in the proportion of subjects (40%) between placebo and the active adalimumab dose group who would experience disease flare assuming a placebo rate of 70% vs. a rate of 30% in the active group. Assuming a binomial distribution, an alpha of 0.05, 80% power, two-sided test, and an initial monotherapy responder rate of 70%, a minimum of 29 subjects were needed per treatment group within the appropriate strata.

Comparison groups	Double-Blind Adalimumab v Double-Blind Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.031
Method	Chi-squared

Secondary: Number of Subjects Meeting Pediatric American College of Rheumatology 30% (PedACR30) Response Criteria at the End of the Open-Label Lead-In Phase

End point title	Number of Subjects Meeting Pediatric American College of Rheumatology 30% (PedACR30) Response Criteria at the End of the Open-Label Lead-In Phase

End point description:

Responders met the following criteria: >= 30% improvement in >= 3 of 6 JRA core set criteria, and >= 30% worsening in not more than 1 JRA criterion, compared with the open-label baseline. JRA core set criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; number of active joints (joints with swelling or with limitation of motion [LOM] and with pain, tenderness or both); number of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. Missing values were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Open-label Adalimumab + MTX	Open-label Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85[3]	86[4]		
Units: subjects	80	64		

Notes:

[3] - All subjects in the ITT population.

[4] - All subjects in the ITT population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in the MTX Stratum With Disease Flare During the Double-Blind Phase

End point title	Number of Subjects in the MTX Stratum With Disease Flare During the Double-Blind Phase

End point description:

Subjects met criteria for disease flare if they had >= 30% worsening in at least 3 of 6 JRA core set criteria and a minimum of 2 active joints, and >= 30% improvement in not more than 1 JRA criterion. JRA core set criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; number of active joints (joints with swelling or with LOM and with pain, tenderness or both); number of joints with LOM; physical function of Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. Missing values were treated as disease flares.

End point type	Secondary

End point timeframe:

Week 16 to Week 48 (32 Weeks)

End point values	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[5]	37[6]		
Units: subjects	14	24		

Notes:

[5] - All subjects in the ITT population in the MTX stratum.

[6] - All subjects in the ITT population in the MTX stratum.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Adalimumab + MTX v Double-Blind Placebo + MTX
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.015
Method	Chi-squared

Secondary: Time to Onset of Disease Flare During the Double-Blind Phase in Subjects in the Non-MTX Stratum

End point title	Time to Onset of Disease Flare During the Double-Blind Phase in Subjects in the Non-MTX Stratum

End point description:

A log rank test was performed and the Kaplan-Meier curve for time to disease flare from double-blind baseline (Week 16) to Week 48 was generated. Disease flare was defined as a >= 30% worsening in at least 3 of 6 JRA core set criteria and a minimum of 2 active joints, and >= 30% improvement in not more than 1 JRA criterion. The percentage of subjects without disease flare at each time point is presented.

End point type	Secondary

End point timeframe:

Week 16 to Week 48 (32 weeks)

End point values	Double-Blind Adalimumab	Double-Blind Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30[7]	28[8]		
Units: percent subjects w/o disease flare				
number (not applicable)				
Week 20	90	78.6		
Week 24	83.3	64.3		
Week 28	80	60.7		
Week 32	70	46.4		
Week 36	66.7	46.4		
Week 40	60	39.3		
Week 44	60	32.1		
Week 48	56.7	28.6		

Notes:

[7] - All subjects in the ITT population in the non-MTX stratum.

[8] - All subjects in the ITT population in the non-MTX stratum.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Adalimumab v Double-Blind Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.029
Method	Logrank

Secondary: Time to Onset of Disease Flare During the Double-Blind Phase in Subjects in the MTX Stratum

End point title	Time to Onset of Disease Flare During the Double-Blind Phase in Subjects in the MTX Stratum

End point description:

A log rank test was performed and the Kaplan-Meier curve for time to disease flare from double-blind

baseline (Week 16) to Week 48 was generated. Disease flare was defined as a >= 30% worsening in at least 3 of 6 JRA core set criteria and a minimum of 2 active joints, and >= 30% improvement in not more than 1 JRA criterion. The percentage of subjects without disease flare at each time point is presented.

End point type	Secondary

End point timeframe:

Week 16 to Week 48 (32 weeks)

End point values	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: percent subjects w/o disease flare				
number (not applicable)				
Week 20	86.8	83.8		
Week 24	78.9	70.3		
Week 28	68.4	59.5		
Week 32	68.4	56.8		
Week 36	63.2	48.6		
Week 40	63.2	45.9		
Week 44	63.2	43.2		
Week 48	63.2	35.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Adalimumab + MTX v Double-Blind Placebo + MTX
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.031
Method	Logrank

Secondary: Number of Subjects Meeting PedACR30 Response Criteria at the End of the Double-Blind Phase

End point title	Number of Subjects Meeting PedACR30 Response Criteria at the End of the Double-Blind Phase

End point description:

Responders met the following criteria: >= 30% improvement in >= 3 of 6 JIA core set criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with the OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; number of active joints (joints with swelling or with LOM and with pain, tenderness or both); number of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core criteria are included in PedACR criteria. Missing values were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[9]	28[10]	38[11]	37[12]
Units: subjects	17	9	24	14

Notes:

[9] - All subjects in the ITT population.

[10] - All subjects in the ITT population.

[11] - All subjects in the ITT population.

[12] - All subjects in the ITT population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Adalimumab v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.061
Method	Pearson's Chi-square test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Adalimumab + MTX v Placebo + MTX
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028
Method	Pearson's Chi-square test

Secondary: Number of Subjects Meeting PedACR50 Response Criteria at the End of the Double-Blind Phase

End point title	Number of Subjects Meeting PedACR50 Response Criteria at the End of the Double-Blind Phase

End point description:

Responders met the following criteria: >= 50% improvement in >= 3 of 6 JIA core set criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with the OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; number of active joints (joints with swelling or with LOM and with pain, tenderness or both); number of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core variables are included in PedACR criteria. Missing values were treated as non-responders.

End point type	Secondary

End point timeframe:
Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[13]	28[14]	38[15]	37[16]
Units: subjects	16	9	24	14

Notes:

[13] - All subjects in the ITT population.

[14] - All subjects in the ITT population.

[15] - All subjects in the ITT population.

[16] - All subjects in the ITT population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Adalimumab
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.103
Method	Pearson's Chi-square test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Adalimumab + MTX v Placebo + MTX
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.028
Method	Pearson's Chi-square test

Secondary: Number of Subjects Meeting PedACR70 Response Criteria at the End of the Double-Blind Phase

End point title	Number of Subjects Meeting PedACR70 Response Criteria at the End of the Double-Blind Phase

End point description:

Responders met the following criteria: >= 70% improvement in >= 3 of 6 JIA core set criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with the OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; number of active joints (joints with swelling or with LOM and with pain, tenderness or both); number of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core variables are included in PedACR criteria. Missing values were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30[17]	28[18]	38[19]	37[20]
Units: subjects	14	8	24	10

Notes:

[17] - All subjects in the ITT population.

[18] - All subjects in the ITT population.

[19] - All subjects in the ITT population.

[20] - All subjects in the ITT population.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Adalimumab v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.156
Method	Pearson's Chi-square test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Adalimumab + MTX v Placebo + MTX
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Pearson's Chi-square test

Secondary: Mean Change From Baseline in Physician's Global Assessment of Disease Activity at Week 48 of the Double-Blind Phase

End point title	Mean Change From Baseline in Physician's Global Assessment of Disease Activity at Week 48 of the Double-Blind Phase

End point description:

A 100 mm horizontal visual analog scale (VAS) was used to assess the Physician Global Assessment of Disease Activity. The left end of the VAS scale (0 mm) signified the absence of symptoms and the right end (100 mm) maximum disease activity. The mean change from open-label baseline to Week 48 was determined. Negative mean changes indicated improvement. Observed data were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[21]	9[22]	24[23]	15[24]
Units: units on a scale				
arithmetic mean (standard error)	-52.06 (± 3.713)	-38.73 (± 6.554)	-48.5 (± 3.89)	-38.73 (± 6.554)

Notes:

[21] - All subjects in the ITT population who remained in the study at Week 48.

[22] - All subjects in the ITT population who remained in the study at Week 48.

[23] - All subjects in the ITT population who remained in the study at Week 48.

[24] - All subjects in the ITT population who remained in the study at Week 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Parent's/Patient's Global Assessment of Disease Activity at Week 48 of the Double-Blind Phase

End point title	Mean Change From Baseline in Parent's/Patient's Global Assessment of Disease Activity at Week 48 of the Double-Blind Phase

End point description:

A 100 mm horizontal visual analog scale (VAS) was used to assess the Parent's/Patient's Global Assessment of Disease Activity. The left end of the VAS (0 mm) signified the absence of symptoms and the right end (100 mm) maximum disease activity. The mean change from open-label baseline to Week 48 was determined. Negative mean changes indicated improvement. Observed data were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[25]	9[26]	24[27]	15[28]
Units: units on a scale				
arithmetic mean (standard error)	-41.53 (± 5.562)	-50.56 (± 6.129)	-36.42 (± 5.177)	-26.87 (± 5.644)

Notes:

[25] - All subjects in the ITT population who completed Week 48.

[26] - All subjects in the ITT population who completed Week 48.

[27] - All subjects in the ITT population who completed Week 48.

[28] - All subjects in the ITT population who completed Week 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in C-Reactive Protein Levels at Week 48 of the Double-Blind Phase

End point title	Mean Change From Baseline in C-Reactive Protein Levels at Week 48 of the Double-Blind Phase

End point description:

Serum levels of C-reactive protein (CRP) were measured at screening (open-label baseline) and at Week 48. Negative mean changes in CRP from open-label baseline to Week 48 indicated improvement. Observed data were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Adalimumab	Placebo	Adalimumab + MTX	Placebo + MTX
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[29]	9[30]	24[31]	15[32]
Units: mg/dL				
arithmetic mean (standard error)	-1.79 (± 0.803)	-3.91 (± 2)	-1.71 (± 0.529)	-0.1 (± 0.333)

Notes:

[29] - All subjects in the ITT population who remained in the study at Week 48.

[30] - All subjects in the ITT population who remained in the study at Week 48.

[31] - All subjects in the ITT population who remained in the study at Week 48.

[32] - All subjects in the ITT population who remained in the study at Week 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Baseline of the Open-Label Extension Body Surface Area Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response Criteria at Baseline of the Open-Label Extension Body Surface Area Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Open-Label Lead-In Phase Baseline

End point values	OLE BSA Adalimumab + MTX	OLE BSA Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[33]	53[34]		
Units: subjects				
PedACR30 Baseline	55	46		
PedACR50 Baseline	47	41		
PedACR70 Baseline	35	30		

Notes:

[33] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

[34] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 56 of the Open-Label Extension Body Surface Area Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 56 of the Open-Label Extension Body Surface Area Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Week 56

End point values	OLE BSA Adalimumab + MTX	OLE BSA Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[35]	41[36]		
Units: subjects				
PedACR30 Week 56	50	40		
PedACR50 Week 56	49	40		
PedACR70 Week 56	43	35		

Notes:

[35] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

[36] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 104 of the Open-Label Extension Body Surface Area Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response

	Criteria at Week 104 of the Open-Label Extension Body Surface Area Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Week 104

End point values	OLE BSA Adalimumab + MTX	OLE BSA Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[37]	17[38]		
Units: subjects				
PedACR30 Week 104	18	16		
PedACR50 Week 104	16	16		
PedACR70 Week 104	14	14		

Notes:

[37] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

[38] - The ITT population was used for analysis in the Open-Label Extension Body Surface Area phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Baseline of the Open-Label Extension Fixed Dose Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response Criteria at Baseline of the Open-Label Extension Fixed Dose Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL-LI baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Baseline

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[39]	45[40]		
Units: subjects				
PedACR30 OLE FD Baseline	53	44		
PedACR50 OLE FD Baseline	50	43		
PedACR70 OLE FD Baseline	46	40		

Notes:

[39] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

[40] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 48 of the Open-Label Extension Fixed Dose Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 48 of the Open-Label Extension Fixed Dose Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL-LI baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Week 48

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[41]	40[42]		
Units: subjects				
PedACR30 Week 48	47	40		
PedACR50 Week 48	47	39		
PedACR70 Week 48	44	38		

Notes:

[41] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

[42] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at Week 112 of the Open-Label Extension Fixed Dose Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response

	Criteria at Week 112 of the Open-Label Extension Fixed Dose Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. All core assessments are included in PedACR criteria.

End point type	Secondary

End point timeframe:

Week 112

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41[43]	31[44]		
Units: subjects				
PedACR30 Week 112	39	31		
PedACR50 Week 112	39	30		
PedACR70 Week 112	34	29		

Notes:

[43] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

[44] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting PedACR30/50/70 Response Criteria at the Final Visit (up to 224 Weeks) of the Open-Label Extension Fixed Dose Phase

End point title	Number of Subjects Meeting PedACR30/50/70 Response Criteria at the Final Visit (up to 224 Weeks) of the Open-Label Extension Fixed Dose Phase

End point description:

Responders met the following criteria: >= 30%/50%/70% improvement in >= 3 of 6 JIA core criteria, and >= 30% worsening in not more than 1 JIA criterion, compared with OL baseline. JIA core criteria included: physician's global assessment of disease severity; parent's/patient's global assessment of overall well-being; # of active joints (joints with swelling or with LOM and with pain, tenderness or both); # of joints with LOM; physical function of the Disability Index of Childhood Health Assessment Questionnaire; C-reactive protein. Final Visit = last visit per subject (up to 224 weeks).

End point type	Secondary

End point timeframe:

Final Visit (up to 224 weeks of OLE FD phase)

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[45]	46[46]		
Units: subjects				
PedACR30 Final Visit	48	44		
PedACR50 Final Visit	45	43		
PedACR70 Final Visit	43	40		

Notes:

[45] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

[46] - The ITT population was used for analysis in the Open-Label Extension Fixed Dose phase.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Measure: Gender, Female/Male - OLE BSA Phase

End point title	Baseline Measure: Gender, Female/Male - OLE BSA Phase

End point description:

Gender (female/male) recorded at Baseline of the Open-Label Extension BSA phase of the study. This measure was excluded from Baseline Characteristics due to difficulty maintaining correct subject numbers and Baseline value totals in that section while including this phase of the study.

End point type	Other pre-specified

End point timeframe:

Baseline OLE BSA Phase

End point values	OLE BSA Adalimumab + MTX	OLE BSA Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	57		
Units: subjects				
OLE BSA Phase - Female	56	42		
OLE BSA Phase - Male	15	15		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Measure: Age Continuous - OLE BSA Phase

End point title	Baseline Measure: Age Continuous - OLE BSA Phase

End point description:

Age continuous (mean +/- SD) recorded at Baseline of the Open-Label Extension BSA phase of the study. This measure was excluded from Baseline Characteristics due to difficulty maintaining correct subject numbers and Baseline value totals in that section with this phase included.

End point type	Other pre-specified

End point timeframe:

Baseline OLE BSA Phase

End point values	OLE BSA Adalimumab + MTX	OLE BSA Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	71	57		
Units: years				
arithmetic mean (standard deviation)	11.3 (± 3.32)	11.2 (± 3.96)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Measure: Gender, Female/Male - OLE FD Phase

End point title	Baseline Measure: Gender, Female/Male - OLE FD Phase

End point description:

Gender (female/male) recorded at Baseline of the Open-Label Extension FD phase of the study. This measure was excluded from Baseline Characteristics due to difficulty maintaining correct subject numbers and Baseline value totals in that section while including this phase of the study.

End point type	Other pre-specified

End point timeframe:

Baseline OLE FD Phase

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	47		
Units: subjects				
OLE FD Phase - Female	45	33		
OLE FD Phase - Male	14	14		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Baseline Measure: Age Continuous - OLE FD Phase

End point title	Baseline Measure: Age Continuous - OLE FD Phase

End point description:

Age continuous (mean +/- SD) recorded at Baseline of the Open-Label Extension FD phase of the study. This measure was excluded from Baseline Characteristics due to difficulty maintaining correct subject numbers and Baseline value totals in that section with this phase included.

End point type	Other pre-specified

End point timeframe:
Baseline OLE FD Phase

End point values	OLE FD Adalimumab + MTX	OLE FD Adalimumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	47		
Units: years				
arithmetic mean (standard deviation)	11.1 (± 3.36)	11 (± 4.12)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

DB Phase - Week 16 to 48 (32 Weeks), Open-Label Extension BSA Phase - OLE BSA Baseline to Week 136 (136 weeks), Open-Label Extension FD Phase - OLE FD Baseline to Final Visit (up to 224 weeks)*
*Last observation of each subject in FD population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Double-Blind Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Reporting group title	Double-Blind Placebo + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum, who had an inadequate response to MTX and were adalimumab responders during the Open-Label Lead-In (OL-LI) phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week) plus concomitant MTX treatment during the Double-Blind Phase of the study. MTX-treated inadequate responders must have had active disease on MTX treatment for at least 3 months prior to screening.

Reporting group title	Double-Blind Adalimumab

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Reporting group title	Double-Blind Placebo

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum who were either naïve to MTX or withdrawn from MTX at least 2 weeks prior to study drug administration, and were adalimumab responders during the OL-LI phase, received placebo (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose, administered subcutaneously every other week), but no concomitant MTX treatment, during the Double-Blind Phase of the study.

Reporting group title	Open-Label Extension BSA Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum received subcutaneous injections of 24 mg adalimumab per square meter of body surface area (BSA) up to a maximum of 40 mg total body dose every other week (eow) concomitantly with MTX treatment during the Open-Label Extension BSA Phase of the study.

Reporting group title	Open-Label Extension BSA Adalimumab

Reporting group description:

Subjects in the non-methotrexate (MTX) stratum received adalimumab (24 mg/square meter of body surface area [BSA], up to a maximum of 40 mg total body dose SC eow) without concomitant MTX treatment during the Open-Label Extension BSA Phase.

Reporting group title	Open-Label Extension FD Adalimumab + MTX

Reporting group description:

Subjects in the methotrexate (MTX) stratum received adalimumab concomitantly with MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study, in which subjects were dosed based on body weight (not BSA). Subjects were separated into 2 body weight categories; subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects

weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Reporting group title	Open-Label Extension FD Adalimumab

Reporting group description:

Subjects in the methotrexate (MTX) stratum received adalimumab without concomitant MTX treatment during the Open-Label Extension (OLE) Fixed Dose (FD) Phase of the study, in which subjects were dosed based on body weight (not BSA). Subjects were separated into 2 body weight categories; subjects weighing less than 30 kg were dosed with 20 mg of adalimumab SC eow, and subjects weighing 30 kg or more were dosed with 40 mg of adalimumab SC eow.

Serious adverse events	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX	Double-Blind Adalimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	2 / 37 (5.41%)	1 / 30 (3.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Abortion spontaneous			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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			
Breast enlargement			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			

subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Nasal septum deviation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Tonsillar hypertrophy			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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			
Bipolar disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Psychotic disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Investigations			
Laboratory test abnormal			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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			
Injury			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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

Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Speech disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Malabsorption			

subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Joint contracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Juvenile arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Knee deformity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Osteoarthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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

Osteochondrosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Spondylolisthesis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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 disorder			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Tendonitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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			
Appendicitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Cervicitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Herpes zoster			

subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Pharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Placebo	Open-Label Extension BSA Adalimumab + MTX	Open-Label Extension BSA Adalimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	13 / 71 (18.31%)	9 / 57 (15.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			

subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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			
Breast enlargement			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Psychotic disorder			

subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Investigations			
Laboratory test abnormal			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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			
Injury			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Joint dislocation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech disorder			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			

subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Haematochezia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malabsorption			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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			
Acne			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint contracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Juvenile arthritis			
subjects affected / exposed	0 / 28 (0.00%)	5 / 71 (7.04%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee deformity			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Osteoarthritis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (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
Osteochondrosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Spondylolisthesis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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 disorder			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Tendonitis			

subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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			
Appendicitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (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
Bronchopneumonia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Herpes zoster			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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
Viral infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetic ketoacidosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (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	Open-Label Extension FD Adalimumab + MTX	Open-Label Extension FD Adalimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 59 (11.86%)	10 / 47 (21.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast enlargement			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nasal septum deviation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Laboratory test abnormal			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericarditis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malabsorption			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile arthritis			
subjects affected / exposed	1 / 59 (1.69%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	1 / 59 (1.69%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rheumatoid arthritis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Double-Blind Adalimumab + MTX	Double-Blind Placebo + MTX	Double-Blind Adalimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 38 (73.68%)	22 / 37 (59.46%)	21 / 30 (70.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Influenza like illness			
subjects affected / exposed	0 / 38 (0.00%)	4 / 37 (10.81%)	0 / 30 (0.00%)
occurrences (all)	0	6	0
Injection site erythema			

subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	2	1	10
Injection site pain			
subjects affected / exposed	7 / 38 (18.42%)	7 / 37 (18.92%)	9 / 30 (30.00%)
occurrences (all)	48	49	45
Injection site reaction			
subjects affected / exposed	7 / 38 (18.42%)	1 / 37 (2.70%)	3 / 30 (10.00%)
occurrences (all)	19	1	11
Pain			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	3 / 30 (10.00%)
occurrences (all)	13	1	9
Pyrexia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	2 / 30 (6.67%)
occurrences (all)	3	1	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Cough			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Rhinitis allergic			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Investigations			

Blood triglycerides increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	7 / 38 (18.42%)	5 / 37 (13.51%)	2 / 30 (6.67%)
occurrences (all)	12	7	2
Excoriation			
subjects affected / exposed	4 / 38 (10.53%)	1 / 37 (2.70%)	3 / 30 (10.00%)
occurrences (all)	10	1	6
Injury			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Joint sprain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Muscle strain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Skin laceration			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Thermal burn			
subjects affected / exposed	1 / 38 (2.63%)	3 / 37 (8.11%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 38 (5.26%)	4 / 37 (10.81%)	2 / 30 (6.67%)
occurrences (all)	3	5	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3

Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	3 / 38 (7.89%)	2 / 37 (5.41%)	0 / 30 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Blister			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Dermatitis contact			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Ecchymosis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Erythema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	4	0	2
Arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Juvenile arthritis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Muscle spasms			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Synovitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Ear infection			

subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Impetigo			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	2
Influenza			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Nasopharyngitis			
subjects affected / exposed	4 / 38 (10.53%)	4 / 37 (10.81%)	0 / 30 (0.00%)
occurrences (all)	4	6	0
Oral herpes			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	0 / 30 (0.00%)
occurrences (all)	1	5	0
Otitis media			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	3	1	0
Paronychia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Pharyngitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	3 / 38 (7.89%)	0 / 37 (0.00%)	2 / 30 (6.67%)
occurrences (all)	3	0	3
Sinusitis			

subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Tonsillitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 38 (15.79%)	4 / 37 (10.81%)	6 / 30 (20.00%)
occurrences (all)	7	5	6
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Viral infection			
subjects affected / exposed	6 / 38 (15.79%)	2 / 37 (5.41%)	6 / 30 (20.00%)
occurrences (all)	7	3	7
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Double-Blind Placebo	Open-Label Extension BSA Adalimumab + MTX	Open-Label Extension BSA Adalimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 28 (71.43%)	63 / 71 (88.73%)	48 / 57 (84.21%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 28 (7.14%)	2 / 71 (2.82%)	3 / 57 (5.26%)
occurrences (all)	2	3	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 28 (3.57%)	2 / 71 (2.82%)	2 / 57 (3.51%)
occurrences (all)	1	2	2
Influenza like illness			
subjects affected / exposed	0 / 28 (0.00%)	4 / 71 (5.63%)	1 / 57 (1.75%)
occurrences (all)	0	5	1
Injection site erythema			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0

Injection site pain			
subjects affected / exposed	3 / 28 (10.71%)	14 / 71 (19.72%)	10 / 57 (17.54%)
occurrences (all)	16	172	108
Injection site reaction			
subjects affected / exposed	1 / 28 (3.57%)	8 / 71 (11.27%)	9 / 57 (15.79%)
occurrences (all)	1	35	30
Pain			
subjects affected / exposed	3 / 28 (10.71%)	0 / 71 (0.00%)	3 / 57 (5.26%)
occurrences (all)	23	0	10
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)	4 / 71 (5.63%)	6 / 57 (10.53%)
occurrences (all)	1	6	6
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	2 / 57 (3.51%)
occurrences (all)	0	2	3
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 28 (3.57%)	2 / 71 (2.82%)	3 / 57 (5.26%)
occurrences (all)	1	6	3
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	3
Cough			
subjects affected / exposed	1 / 28 (3.57%)	6 / 71 (8.45%)	5 / 57 (8.77%)
occurrences (all)	1	6	6
Oropharyngeal pain			
subjects affected / exposed	1 / 28 (3.57%)	6 / 71 (8.45%)	0 / 57 (0.00%)
occurrences (all)	1	6	0
Rhinitis allergic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	2
Investigations			
Blood triglycerides increased			

subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 28 (7.14%)	4 / 71 (5.63%)	2 / 57 (3.51%)
occurrences (all)	3	4	2
Contusion			
subjects affected / exposed	2 / 28 (7.14%)	4 / 71 (5.63%)	3 / 57 (5.26%)
occurrences (all)	5	4	5
Excoriation			
subjects affected / exposed	1 / 28 (3.57%)	7 / 71 (9.86%)	4 / 57 (7.02%)
occurrences (all)	1	12	4
Injury			
subjects affected / exposed	4 / 28 (14.29%)	3 / 71 (4.23%)	1 / 57 (1.75%)
occurrences (all)	4	4	1
Joint sprain			
subjects affected / exposed	3 / 28 (10.71%)	1 / 71 (1.41%)	4 / 57 (7.02%)
occurrences (all)	3	1	6
Muscle strain			
subjects affected / exposed	1 / 28 (3.57%)	1 / 71 (1.41%)	4 / 57 (7.02%)
occurrences (all)	1	1	4
Skin laceration			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	0 / 57 (0.00%)
occurrences (all)	0	4	0
Thermal burn			
subjects affected / exposed	1 / 28 (3.57%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 28 (14.29%)	9 / 71 (12.68%)	8 / 57 (14.04%)
occurrences (all)	10	13	11
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	2
Eye disorders			

Conjunctivitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	4 / 57 (7.02%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 28 (7.14%)	3 / 71 (4.23%)	1 / 57 (1.75%)
occurrences (all)	3	3	1
Abdominal pain upper			
subjects affected / exposed	1 / 28 (3.57%)	0 / 71 (0.00%)	1 / 57 (1.75%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	9 / 71 (12.68%)	3 / 57 (5.26%)
occurrences (all)	1	15	6
Vomiting			
subjects affected / exposed	1 / 28 (3.57%)	5 / 71 (7.04%)	3 / 57 (5.26%)
occurrences (all)	1	5	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 28 (3.57%)	3 / 71 (4.23%)	2 / 57 (3.51%)
occurrences (all)	1	3	2
Blister			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 28 (0.00%)	5 / 71 (7.04%)	0 / 57 (0.00%)
occurrences (all)	0	5	0
Ecchymosis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	1 / 57 (1.75%)
occurrences (all)	0	2	1
Eczema			
subjects affected / exposed	1 / 28 (3.57%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences (all)	3	0	0
Rash			

subjects affected / exposed	0 / 28 (0.00%)	5 / 71 (7.04%)	4 / 57 (7.02%)
occurrences (all)	0	5	4
Erythema			
subjects affected / exposed	2 / 28 (7.14%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 28 (3.57%)	5 / 71 (7.04%)	6 / 57 (10.53%)
occurrences (all)	1	7	9
Arthritis			
subjects affected / exposed	1 / 28 (3.57%)	3 / 71 (4.23%)	1 / 57 (1.75%)
occurrences (all)	1	3	1
Juvenile arthritis			
subjects affected / exposed	1 / 28 (3.57%)	2 / 71 (2.82%)	3 / 57 (5.26%)
occurrences (all)	1	3	3
Muscle spasms			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	3 / 57 (5.26%)
occurrences (all)	0	1	3
Pain in extremity			
subjects affected / exposed	2 / 28 (7.14%)	4 / 71 (5.63%)	0 / 57 (0.00%)
occurrences (all)	2	4	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 28 (0.00%)	7 / 71 (9.86%)	7 / 57 (12.28%)
occurrences (all)	0	11	8
Synovitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	0 / 57 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 28 (0.00%)	4 / 71 (5.63%)	0 / 57 (0.00%)
occurrences (all)	0	6	0
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)	4 / 71 (5.63%)	2 / 57 (3.51%)
occurrences (all)	1	5	2
Ear infection			

subjects affected / exposed	1 / 28 (3.57%)	4 / 71 (5.63%)	0 / 57 (0.00%)
occurrences (all)	1	4	0
Gastroenteritis viral			
subjects affected / exposed	1 / 28 (3.57%)	1 / 71 (1.41%)	2 / 57 (3.51%)
occurrences (all)	1	1	2
Herpes virus infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 71 (1.41%)	0 / 57 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	5 / 57 (8.77%)
occurrences (all)	0	3	5
Influenza			
subjects affected / exposed	2 / 28 (7.14%)	2 / 71 (2.82%)	4 / 57 (7.02%)
occurrences (all)	2	2	4
Nasopharyngitis			
subjects affected / exposed	3 / 28 (10.71%)	8 / 71 (11.27%)	4 / 57 (7.02%)
occurrences (all)	4	9	6
Oral herpes			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	2 / 57 (3.51%)
occurrences (all)	0	3	3
Otitis media			
subjects affected / exposed	0 / 28 (0.00%)	2 / 71 (2.82%)	5 / 57 (8.77%)
occurrences (all)	0	2	6
Paronychia			
subjects affected / exposed	1 / 28 (3.57%)	3 / 71 (4.23%)	1 / 57 (1.75%)
occurrences (all)	1	3	1
Pharyngitis			
subjects affected / exposed	1 / 28 (3.57%)	9 / 71 (12.68%)	4 / 57 (7.02%)
occurrences (all)	1	12	4
Pharyngitis streptococcal			
subjects affected / exposed	1 / 28 (3.57%)	3 / 71 (4.23%)	6 / 57 (10.53%)
occurrences (all)	1	3	8
Rhinitis			
subjects affected / exposed	0 / 28 (0.00%)	4 / 71 (5.63%)	2 / 57 (3.51%)
occurrences (all)	0	4	3
Sinusitis			

subjects affected / exposed	1 / 28 (3.57%)	7 / 71 (9.86%)	7 / 57 (12.28%)
occurrences (all)	2	8	10
Tonsillitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 71 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	5 / 28 (17.86%)	21 / 71 (29.58%)	19 / 57 (33.33%)
occurrences (all)	6	34	40
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)	5 / 71 (7.04%)	4 / 57 (7.02%)
occurrences (all)	1	6	4
Viral infection			
subjects affected / exposed	3 / 28 (10.71%)	13 / 71 (18.31%)	9 / 57 (15.79%)
occurrences (all)	3	22	12
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)	3 / 71 (4.23%)	4 / 57 (7.02%)
occurrences (all)	1	3	6

Non-serious adverse events	Open-Label Extension FD Adalimumab + MTX	Open-Label Extension FD Adalimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 59 (91.53%)	38 / 47 (80.85%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 59 (3.39%)	3 / 47 (6.38%)	
occurrences (all)	4	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 59 (5.08%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Influenza like illness			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	

Injection site pain			
subjects affected / exposed	4 / 59 (6.78%)	4 / 47 (8.51%)	
occurrences (all)	8	6	
Injection site reaction			
subjects affected / exposed	2 / 59 (3.39%)	1 / 47 (2.13%)	
occurrences (all)	2	2	
Pain			
subjects affected / exposed	0 / 59 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	2 / 59 (3.39%)	5 / 47 (10.64%)	
occurrences (all)	3	5	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 59 (3.39%)	3 / 47 (6.38%)	
occurrences (all)	2	4	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 59 (5.08%)	0 / 47 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 59 (1.69%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	2 / 59 (3.39%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Oropharyngeal pain			
subjects affected / exposed	4 / 59 (6.78%)	0 / 47 (0.00%)	
occurrences (all)	4	0	
Rhinitis allergic			
subjects affected / exposed	3 / 59 (5.08%)	0 / 47 (0.00%)	
occurrences (all)	5	0	
Investigations			
Blood triglycerides increased			

subjects affected / exposed	3 / 59 (5.08%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 59 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	3	
Contusion			
subjects affected / exposed	1 / 59 (1.69%)	4 / 47 (8.51%)	
occurrences (all)	1	6	
Excoriation			
subjects affected / exposed	2 / 59 (3.39%)	4 / 47 (8.51%)	
occurrences (all)	2	7	
Injury			
subjects affected / exposed	1 / 59 (1.69%)	4 / 47 (8.51%)	
occurrences (all)	1	6	
Joint sprain			
subjects affected / exposed	1 / 59 (1.69%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Muscle strain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 59 (6.78%)	11 / 47 (23.40%)	
occurrences (all)	4	21	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	2 / 59 (3.39%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 59 (8.47%)	4 / 47 (8.51%)	
occurrences (all)	5	6	
Abdominal pain upper			
subjects affected / exposed	1 / 59 (1.69%)	4 / 47 (8.51%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	2 / 59 (3.39%)	6 / 47 (12.77%)	
occurrences (all)	4	8	
Vomiting			
subjects affected / exposed	2 / 59 (3.39%)	3 / 47 (6.38%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 59 (5.08%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Blister			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Dermatitis contact			
subjects affected / exposed	3 / 59 (5.08%)	4 / 47 (8.51%)	
occurrences (all)	3	4	
Ecchymosis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Rash			

subjects affected / exposed	2 / 59 (3.39%)	6 / 47 (12.77%)	
occurrences (all)	2	7	
Erythema			
subjects affected / exposed	1 / 59 (1.69%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 59 (6.78%)	7 / 47 (14.89%)	
occurrences (all)	7	12	
Arthritis			
subjects affected / exposed	4 / 59 (6.78%)	7 / 47 (14.89%)	
occurrences (all)	5	10	
Juvenile arthritis			
subjects affected / exposed	4 / 59 (6.78%)	4 / 47 (8.51%)	
occurrences (all)	5	5	
Muscle spasms			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	1 / 59 (1.69%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Rheumatoid arthritis			
subjects affected / exposed	7 / 59 (11.86%)	6 / 47 (12.77%)	
occurrences (all)	11	10	
Synovitis			
subjects affected / exposed	0 / 59 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	4	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	6 / 59 (10.17%)	0 / 47 (0.00%)	
occurrences (all)	10	0	
Bronchitis			
subjects affected / exposed	1 / 59 (1.69%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Ear infection			

subjects affected / exposed	7 / 59 (11.86%)	3 / 47 (6.38%)	
occurrences (all)	7	3	
Gastroenteritis viral			
subjects affected / exposed	3 / 59 (5.08%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Herpes virus infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Impetigo			
subjects affected / exposed	0 / 59 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	3 / 59 (5.08%)	5 / 47 (10.64%)	
occurrences (all)	3	5	
Nasopharyngitis			
subjects affected / exposed	7 / 59 (11.86%)	3 / 47 (6.38%)	
occurrences (all)	7	3	
Oral herpes			
subjects affected / exposed	3 / 59 (5.08%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Otitis media			
subjects affected / exposed	3 / 59 (5.08%)	1 / 47 (2.13%)	
occurrences (all)	3	2	
Paronychia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	6 / 59 (10.17%)	1 / 47 (2.13%)	
occurrences (all)	9	1	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 59 (1.69%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Rhinitis			
subjects affected / exposed	3 / 59 (5.08%)	4 / 47 (8.51%)	
occurrences (all)	6	5	
Sinusitis			

subjects affected / exposed	7 / 59 (11.86%)	3 / 47 (6.38%)	
occurrences (all)	7	4	
Tonsillitis			
subjects affected / exposed	3 / 59 (5.08%)	2 / 47 (4.26%)	
occurrences (all)	3	5	
Upper respiratory tract infection			
subjects affected / exposed	15 / 59 (25.42%)	13 / 47 (27.66%)	
occurrences (all)	23	27	
Urinary tract infection			
subjects affected / exposed	5 / 59 (8.47%)	2 / 47 (4.26%)	
occurrences (all)	10	2	
Viral infection			
subjects affected / exposed	15 / 59 (25.42%)	8 / 47 (17.02%)	
occurrences (all)	17	11	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 59 (3.39%)	2 / 47 (4.26%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2002	To clarify that subjects who respond to treatment with adalimumab will be randomized at Week 16; all sites will develop their institution-specific informed consent form.
26 September 2002	To add an additional pharmacokinetic blood sample to be taken between Day 2 and Day 10 after the first dose of adalimumab; to incorporate the open-label extension study (subjects who complete 48 weeks of treatment or are withdrawn from the double-blind phase due to disease flare were eligible).
03 July 2003	To expand the safety assessments to include a serum pregnancy on all females aged 10 years and older at all visits, and clarify the visit schedule for the OL extension portion.
05 February 2004	To extend the OL extension portion of study to up to 5 years or 60 days post marketing approval in each country; clarify which study visits require a blinded joint assessor, clarify the requirements for chest X-rays and/or PPD skin tests in Europe; clarify the study visit window schedule.
26 August 2005	To switch subjects from a dose of study medication based on BSA to a fixed dose of study drug (20 or 40 mg eow based on weight); remove Post Study Visit (Follow-Up); update the schedule for drug administration at the study site; amend study visit schedule to allow for pharmacokinetic sampling and validate safety and efficacy of new fixed dosing regimen; clarify that the DSMB will not participate in the OL portion of the trial; change the evaluation time period for joints injected with intra-articular and/or soft-tissue corticosteroids from non-evaluable for the duration of the study to evaluable after 3 months;
01 April 2009	To extend the fixed dose portion of the study to 244 weeks to accommodate patients in Europe who are not yet able to receive drug commercially because of their age; and add 4 additional visits to the OL Fixed Dose.
24 September 2009	To update the protocol to reflect the renaming and reclassification of juvenile rheumatoid arthritis (JRA) to juvenile idiopathic arthritis (JIA); clarify study visits and procedures for subjects in the EU who will be continuing in the study past Fixed Dose Week 176; update conditions in which a subject should be withdrawn for safety reasons; update introduction, CTC Grading Severity of Adverse Events version, excluded medications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported