Clinical trial results:
A Multicenter, Open-label 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	2014-004558-33
Trial protocol	Outside EU/EEA
Global end of trial date	05 September 2011

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	M10-240

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00690573
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	Shigeki Hashimoto, AbbVie, shigeki.hashimoto@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy, safety and pharmacokinetics of adalimumab in Japanese children with Polyarticular Juvenile Rheumatoid Arthritis

Protection of trial subjects:

Subject and/or legal guardian read and understood information provided about the study and gave written permission. If a subject had an ability to provide an assent to participating in the clinical trial, the subject provided written informed assent. If a subject could not provide his/her signature, the investigator or clinical trial support staff confirmed the subject's willingness and recorded it.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 25
Worldwide total number of subjects	25
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	8
Adolescents (12-17 years)	17
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adalimumab dose was determined by baseline body weight (20 mg for subjects weighing < 30 kg, 40 mg for subjects weighing 30 kg or more) through Week 14. After Week 16, dose was based on body weight measured at Week 16 and every 12 weeks. Twenty subjects received concomitant methotrexate therapy during the study.

Period 1

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

Arms

Arm title	Adalimumab

Arm description:

Adalimumab administered subcutaneously every other week, with dosage determined by body weight at study entry (20 mg for children weighing less than 30 kg, 40 mg for children weighing 30 kg or more).

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

Dosage and administration details:

Adalimumab administered subcutaneously every other week, with dosage determined by body weight at study entry (20 mg for children weighing less than 30 kg, 40 mg for children weighing 30 kg or more).

Number of subjects in period 1	Adalimumab
Started	25
Completed	16
Not completed	9
Consent withdrawn by subject	1
Lack of efficacy	8

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab administered subcutaneously every other week, with dosage determined by body weight at study entry (20 mg for children weighing less than 30 kg, 40 mg for children weighing 30 kg or more).	

Reporting group values	Adalimumab	Total	
Number of subjects	25	25	
Age Categorical Units: participants			
<=18 years	25	25	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	13		
standard deviation	± 3.38	-	
Gender, Male/Female Units: participants			
Female	20	20	
Male	5	5	

End points

End points reporting groups

Reporting group title	Adalimumab

Reporting group description:

Adalimumab administered subcutaneously every other week, with dosage determined by body weight at study entry (20 mg for children weighing less than 30 kg, 40 mg for children weighing 30 kg or more).

Primary: Number of subjects achieving Pediatric American College of Rheumatology 30% (PedACR30) Response at Week 16

End point title	Number of subjects achieving Pediatric American College of Rheumatology 30% (PedACR30) Response at Week 16[1]

End point description:

Response defined as at least 30% improvement in 3 or more of 6 juvenile rheumatoid arthritis (JRA) core set criteria, and at least 30% worsening in not more than 1 JRA criterion, compared with baseline. JRA core set criteria include 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. The analysis was conducted using the full analysis set (FAS) population, which was defined as all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Week 16

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive data are summarized for this end point per protocol.

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
number (not applicable)	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects achieving PedACR50 and PedACR70 Responses at Week 16

End point title	Number of subjects achieving PedACR50 and PedACR70 Responses at Week 16

End point description:

Response defined as at least 50/70% improvement in 3 or more of 6 juvenile rheumatoid arthritis (JRA) core set criteria, and at least 50/70% worsening in not more than 1 JRA criterion compared with baseline. JRA core set criteria include 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. The analysis was conducted using the FAS population. Missing values were treated as non-

responders.

End point type	Secondary

End point timeframe:

Week 16

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
number (not applicable)				
Number of Subjects Achieving PedACR50 at Week 16	22			
Number of Subjects Achieving PedACR70 at Week 16	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving PedACR 30/50/70 Responses

End point title	Number of Subjects Achieving PedACR 30/50/70 Responses

End point description:

The analysis was conducted using the full analysis set FAS population as observed. N=25 at Weeks 2, 4, and the Final Visit; N=24 at Weeks 8, 24, and 36; N=23 at Week 48; N=22 at Week 60; N=19 at Weeks 72 and 96; N=11 at Week 120; and N=5 at Week 144.

End point type	Secondary

End point timeframe:

Week 2, 4, 8, and 24, every 12 weeks from Week 24 to Week 60, and every 24 weeks from Week 72 to the final visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
number (not applicable)				
Number of subjects achieving PedACR30 at Week 2	15			
Number of subjects achieving PedACR30 at Week 4	16			
Number of subjects achieving PedACR30 at Week 8	19			
Number of subjects achieving PedACR30 at Week 24	21			
Number of subjects achieving PedACR30 at Week 36	22			

Number of subjects achieving PedACR30 at Week 48	21			
Number of subjects achieving PedACR30 at Week 60	20			
Number of subjects achieving PedACR30 at Week 72	19			
Number of subjects achieving PedACR30 at Week 96	18			
Number of subjects achieving PedACR30 at Week 120	11			
Number of subjects achieving PedACR30 at Week 144	5			
Number of subjects achieving PedACR30- Final Visit	22			
Number of subjects achieving PedACR50 at Week 2	7			
Number of subjects achieving PedACR50 at Week 4	13			
Number of subjects achieving PedACR50 at Week 8	15			
Number of subjects achieving PedACR50 at Week 24	19			
Number of subjects achieving PedACR50 at Week 36	22			
Number of subjects achieving PedACR50 at Week 48	19			
Number of subjects achieving PedACR50 at Week 60	20			
Number of subjects achieving PedACR50 at Week 72	18			
Number of subjects achieving PedACR50 at Week 96	18			
Number of subjects achieving PedACR50 at Week 120	11			
Number of subjects achieving PedACR50 at Week 144	5			
Number of subjects achieving PedACR50- Final Visit	20			
Number of subjects achieving PedACR70 at Week 2	1			
Number of subjects achieving PedACR70 at Week 4	7			
Number of subjects achieving PedACR70 at Week 8	8			
Number of subjects achieving PedACR70 at Week 24	15			
Number of subjects achieving PedACR70 at Week 36	19			
Number of subjects achieving PedACR70 at Week 48	17			
Number of subjects achieving PedACR70 at Week 60	16			
Number of subjects achieving PedACR70 at Week 72	15			
Number of subjects achieving PedACR70 at Week 96	14			
Number of subjects achieving PedACR70 at Week 120	11			
Number of subjects achieving PedACR70 at Week 144	5			
Number of subjects achieving PedACR70- Final Visit	17			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean serum adalimumab concentration

End point title	Mean serum adalimumab concentration

End point description:

Blood samples were drawn prior to drug administration. Adalimumab concentrations in serum were determined using a validated enzyme-linked immunosorbent assay (ELISA) method based on a double-antigen technique. Concentrations are reported as micrograms per milliliter (mcg/mL). For the 20 mg dose, N = 8 at each timepoint. For the 40 mg dose, N = 17 at Weeks 2 and 4; N = 16 at Weeks 8, 16, and 24; N = 14 at Week 36; N = 15 at Week 48; and N = 14 at Week 60.

End point type	Secondary

End point timeframe:

Week 2, 4, 8, 16, and 24, and every 12 weeks up to Week 60

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: mcg/mL				
arithmetic mean (standard deviation)				
20 mg dose at Week 2	5.24 (± 1.74)			
20 mg dose at Week 4	5.46 (± 5.18)			
20 mg dose at Week 8	6.15 (± 5.88)			
20 mg dose at Week 16	5.73 (± 5.26)			
20 mg dose at Week 24	5.79 (± 6.51)			
20 mg dose at Week 36	7.6 (± 7.58)			
20 mg dose at Week 48	7.97 (± 6.69)			
20 mg dose at Week 60	11.4 (± 9.87)			
40 mg dose at Week 2	5.03 (± 1.45)			
40 mg dose at Week 4	5.63 (± 2.71)			
40 mg dose at Week 8	8.66 (± 4.41)			
40 mg dose at Week 16	10.8 (± 6.15)			
40 mg dose at Week 24	11.9 (± 6.8)			
40 mg dose at Week 36	12.6 (± 6.44)			
40 mg dose at Week 48	13 (± 8.89)			
40 mg dose at Week 60	13.1 (± 6.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects positive for anti-adalimumab antibodies (AAA)

End point title	Number of subjects positive for anti-adalimumab antibodies (AAA)

End point description:

Serum samples with adalimumab concentration below 2 mcg/mL were selected for AAA analyses. Samples were considered AAA positive if the measured AAA concentration was above 20 ng/mL. A subject was considered to be AAA positive if the subject had at least one AAA positive sample observed within 30 days following the subject's last adalimumab dose.

End point type	Secondary

End point timeframe:

Week 24 and Week 60

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
number (not applicable)				
Number of subjects with AAA by Week 24	4			
Number of subjects with AAA by Week 60	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events reported from the time of first study drug administration until 70 days following discontinuation of study drug administration were collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Adalimumab

Reporting group description:

Adalimumab administered subcutaneously every other week, with dosage determined by body weight at study entry (20 mg for children weighing less than 30 kg, 40 mg for children weighing 30 kg or more).

Serious adverse events	Adalimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Juvenile arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Hepatitis B			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adalimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
General disorders and administration site conditions			
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Injection site reaction			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	6		
Immune system disorders			
Seasonal allergy			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Cough			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Pharyngolaryngeal pain			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Rhinitis allergic			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Rhinorrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Investigations			
Antinuclear antibody positive			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
DNA antibody positive			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Contusion			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hand fracture			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Joint sprain			

alternative assessment type: Systematic subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 5		
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 16		
Blood and lymphatic system disorders Iron deficiency anaemia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 6		
Eye disorders Conjunctivitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 4		
Conjunctivitis allergic alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Keratoconjunctivitis sicca alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Gastrointestinal disorders Abdominal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Abdominal pain upper alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Constipation			

alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dental caries alternative assessment type: Systematic subjects affected / exposed occurrences (all) Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all) Stomatitis alternative assessment type: Systematic subjects affected / exposed occurrences (all) Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 4 3 / 25 (12.00%) 3 3 / 25 (12.00%) 3 3 / 25 (12.00%) 3 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2		
Hepatobiliary disorders Hepatic function abnormal alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Skin and subcutaneous tissue disorders Acne alternative assessment type: Systematic subjects affected / exposed occurrences (all) Dermatitis atopic alternative assessment type: Systematic	2 / 25 (8.00%) 2		

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Dermatitis bullous			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Eczema			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	7		
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Urticaria			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Juvenile arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Infections and infestations			
Gastroenteritis			
alternative assessment type: Systematic			

subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	10		
Hordeolum			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Impetigo			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	8		
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 25 (56.00%)		
occurrences (all)	33		
Oral herpes			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Pharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	12		
Upper respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 25 (56.00%)		
occurrences (all)	38		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2008	- Updated the approval status of adalimumab. - Added the procedure to confirm subject's safety after the dose escalation. - Added the detailed explanation about when MTX dose was changed before the enrollment to the procedure for eligibility confirmation. - Changed the timing to conduct chest X-ray. - Changed the contact information of the sponsor.
02 February 2009	- Changed the amount of MTX described in inclusion criteria #2 from 10 mg/m^2/week to 8 to 10 mg/m^2/week to relax this inclusion criterion. - Updated the approval status of adalimumab. - Extended the enrollment period.
22 June 2009	- Added the criteria for interruption due to clinical remission. - Changed the procedure of the protocol deviation. - Changed the medical expert and adalimumab concentration assay institution.
10 September 2010	- Deleted the section for Dose escalation
27 May 2011	- Added the follow-up test at approval.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported