Clinical trial results:
A Phase 2b, Multicenter, Open-Label Study in Rheumatoid Arthritis Subjects who Completed Preceding Study M13-390 with Adalimumab

Summary

EudraCT number	2012-003881-42
Trial protocol	BE DE RO SK
Global end of trial date	22 October 2013

Results information

Result version number	v2 (current)
This version publication date	18 May 2016
First version publication date	14 June 2015
Version creation reason	• Correction of full data set potential category issues

Trial information

Trial identification

Sponsor protocol code	M13-692

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01752855
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	Abbott House, Vanwall Business Park Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL64XE
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	Andy Payne, AbbVie , andy.payne@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A Phase 2b, open-label extension (OLE) study in rheumatoid arthritis (RA) patients designed to collect long-term safety, tolerability, efficacy, and immunogenicity data of the proposed new adalimumab formulation.

Protection of trial subjects:

- Only participants that met all the study inclusion and none of the exclusion criteria were allowed entry into the study.
- Participants read and understood information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2012
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	Slovakia: 17
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	88
EEA total number of subjects	56

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	71
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 96 subjects who completed Study M13-390, 88 subjects (92%, 88/96) enrolled in the OLE Study M13-692 at 20 study sites located in North America and Europe.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	New Formulation for 48 weeks

Arm description:

New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

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

Dosage and administration details:

Subcutaneous injection of the new formulation of adalimumab 40 mg every other week for 24 weeks

Arm title	Current Formulation for 24 Weeks, New Formulation for 24 Weeks

Arm description:

Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

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

Dosage and administration details:

Subcutaneous injection of the new formulation of adalimumab 40 mg every other week for 24 weeks

Number of subjects in period 1	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks
Started	44	44
Completed	43	40
Not completed	1	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	-
Lack of efficacy	-	2

Baseline characteristics

Reporting groups

Reporting group title	New Formulation for 48 weeks
Reporting group description:	
New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week	
Reporting group title	Current Formulation for 24 Weeks, New Formulation for 24 Weeks
Reporting group description:	
Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week	

Reporting group values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks	Total
Number of subjects	44	44	88
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	55.7	52	
standard deviation	± 10.8	± 12	-
Gender categorical			
Units: Subjects			
Female	37	37	74
Male	7	7	14

Subject analysis sets

Subject analysis set title	Overall Study
Subject analysis set type	Full analysis
Subject analysis set description:	
The study population consisted of all randomized subjects who received at least one dose of adalimumab. All randomized subjects were included in the analyses.	

Reporting group values	Overall Study		
Number of subjects	88		

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	53.9		
standard deviation	± 11.5		
Gender categorical Units: Subjects			
Female	74		
Male	14		

End points

End points reporting groups

Reporting group title	New Formulation for 48 weeks

Reporting group description:

New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

Reporting group title	Current Formulation for 24 Weeks, New Formulation for 24 Weeks

Reporting group description:

Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

Subject analysis set title	Overall Study
Subject analysis set type	Full analysis

Subject analysis set description:

The study population consisted of all randomized subjects who received at least one dose of adalimumab. All randomized subjects were included in the analyses.

Primary: Mean Change From Baseline in Disease Activity Score 28 (DAS28) at Weeks 36 and 48

End point title	Mean Change From Baseline in Disease Activity Score 28 (DAS28) at Weeks 36 and 48[1]

End point description:

The Disease Activity Score (DAS28) is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, C-reactive protein, and general health are included in the DAS28 score. Scores on the DAS28 range from 0 to 10. A DAS28 score >5.1 indicates high disease activity, a DAS28 score <3.2 indicates low disease activity, and a DAS28 score <2.6 indicates clinical remission.

End point type	Primary

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

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: Within-group analyses:(Mean change [2-sided 95%CI]) for New Formulation for 48 wks from baseline to Wk 36: -2.4 (-2.7, -2); (Mean change [2-sided 95%CI]) for New Formulation for 48 wks-from baseline to Wk 48: -2.4 (-2.8, -2); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 36: -2.2 (-2.5, -1.9); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 48: -2.3 (-2.7, -1.9)

End point values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[2]	44[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 36	-2.4 (± 1.17)	-2.2 (± 1.05)		
Week 48	-2.4 (± 1.29)	-2.2 (± 1.28)		

Notes:

[2] - All available data were included. The last available values were used to replace any missing values.

[3] - All available data were included. The last available values were used to replace any missing values.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology (ACR) 20 Response at Weeks 36 and 48

End point title	Percentage of Participants With an American College of Rheumatology (ACR) 20 Response at Weeks 36 and 48[4]

End point description:

American College of Rheumatology 20% (ACR20) response. A participant is a responder if the following 3 criteria for improvement from baseline are met:
≥ 20% improvement in tender joint count;
≥ 20% improvement in swollen joint count; and
≥ 20% improvement in at least 3 of the 5 following parameters:
- Physician global assessment of disease activity
- Patient global assessment of disease activity
- Patient assessment of pain
- Disability Index of the Health Assessment
- CRP (Acute phase reactant (Erythrocyte sedimentation rate/C-reactive protein))

End point type	Primary

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

Notes:

[4] - 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: Within-group analyses: (Percentage [2-sided 95%CI]) for New Formulation for 48 wks at Week 36: (72.7 (57.2, 85); (Percentage [2-sided 95%CI]) for New Formulation for 48 Wks at Week 48: 74.4 (58.8, 86.5); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 36: 76.7 (61.4, 88.2); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 48: 80 (64.4, 90.9)

End point values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[5]	44[6]		
Units: percentage of participants				
number (not applicable)				
Week 36	72.7	76.7		
Week 48	74.4	80		

Notes:

[5] - All participants who received at least one dose of study drug

[6] - All participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology (ACR) 50 Response at Weeks 36 and 48

End point title	Percentage of Participants With an American College of Rheumatology (ACR) 50 Response at Weeks 36 and 48[7]

End point description:

American College of Rheumatology 50% (ACR50) response. A participant is a responder if the following 3 criteria for improvement from baseline are met:
≥ 50% improvement in tender joint count;

≥ 50% improvement in swollen joint count; and
≥ 50% improvement in at least 3 of the 5 following parameters:
o Physician global assessment of disease activity
o Patient global assessment of disease activity
o Patient assessment of pain
o Disability Index of the Health Assessment
o CRP (Acute phase reactant (Erythrocyte sedimentation rate/C-reactive protein))

End point type	Primary

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

Notes:

[7] - 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: Within-group analyses: (Percentage [2-sided 95%CI]) for New Formulation for 48 wks at Week 36: (50 (34.6, 65.4); (Percentage [2-sided 95%CI]) for New Formulation for 48 Wks at Week 48: 53.5 (37.7, 68.8); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 36: 51.2 (35.5, 66.7); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 48: 57.5 (40.9, 73.0)

End point values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[8]	44[9]		
Units: percentage of participants				
number (not applicable)				
Week 36	50	51.2		
Week 48	53.5	57.5		

Notes:

[8] - All participants who received at least one dose of study drug

[9] - All participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in Health Assessment Questionnaire (HAQ-DI) at Weeks 36 and 48

End point title	Mean Change From Baseline in Health Assessment Questionnaire (HAQ-DI) at Weeks 36 and 48[10]

End point description:

The Health Assessment Questionnaire - Disability Index (HAQ-DI) is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task were summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. The minimal clinically important difference (MCID) defined for the HAQ-DI is 0.22. HAQ remission indicating normal physical function is defined by HAQ-DI < 0.5.

End point type	Primary

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

Notes:

[10] - 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: Within-group analyses:(Mean change [2-sided 95%CI]) for New Formulation for 48 wks from baseline to Wk 36: -0.5 (–0.7, –0.3); (Mean change [2-sided 95%CI]) for New Formulation for 48 wks-from baseline to Wk 48: -0.5 (–0.7, –0.4); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 36: -0.5 (–0.7, –0.3); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 48: -0.5 (–0.7, -0.3)

End point values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[11]	43[12]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 36	-0.5 (± 0.6)	-0.5 (± 0.69)		
Week 48	-0.5 (± 0.57)	-0.5 (± 0.58)		

Notes:

[11] - Data were analyzed for 44 and 43 participants, respectively, at weeks 36 and 48.

[12] - Data were analyzed for 43 participants at week 36 and 40 participants at week 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive for Anti-adalimumab Antibody

End point title	Percentage of Participants Positive for Anti-adalimumab Antibody
End point description:	
Percentage of participants with anti-adalimumab antibody	
End point type	Secondary
End point timeframe:	
Week 24 through Week 48	

End point values	New Formulation for 48 weeks	Current Formulation for 24 Weeks, New Formulation for 24 Weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[13]	44[14]		
Units: percentage of participants				
number (not applicable)	13.6	18.2		

Notes:

[13] - All participants who received at least one dose of study drug

[14] - All participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of study drug administration until 70 days following the last dose, approximately 58 weeks. Serious adverse events were collected from the time the participant signed the informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Current Formulation for 24 Weeks, New Formulation for 24 Weeks

Reporting group description:

Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

Reporting group title	New Formulation for 48 weeks

Reporting group description:

New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

Serious adverse events	Current Formulation for 24 Weeks, New Formulation for 24 Weeks	New Formulation for 48 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	2 / 44 (4.55%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	1 / 44 (2.27%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Current Formulation for 24 Weeks, New Formulation for 24 Weeks	New Formulation for 48 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 44 (43.18%)	18 / 44 (40.91%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 44 (6.82%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 44 (6.82%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	3 / 44 (6.82%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 44 (6.82%)	0 / 44 (0.00%)	
occurrences (all)	3	0	
Rheumatoid arthritis			
subjects affected / exposed	4 / 44 (9.09%)	3 / 44 (6.82%)	
occurrences (all)	5	3	
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 44 (4.55%)	4 / 44 (9.09%)	
occurrences (all)	3	7	
Nasopharyngitis			

subjects affected / exposed	7 / 44 (15.91%)	6 / 44 (13.64%)	
occurrences (all)	12	10	
Oral herpes			
subjects affected / exposed	2 / 44 (4.55%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Upper respiratory tract Infection			
subjects affected / exposed	4 / 44 (9.09%)	4 / 44 (9.09%)	
occurrences (all)	4	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported