Clinical trial results:
Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis: an open-label extension trial for patients who have completed Trial 1297.2 and are eligible for long-term treatment with adalimumab.

Summary

EudraCT number	2015-002634-41
Trial protocol	HU ES DE PL BG
Global end of trial date	01 November 2017

Results information

Result version number	v2 (current)
This version publication date	14 November 2021
First version publication date	15 November 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1297.3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02640612
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	21 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2017
Global end of trial reached?	Yes
Global end of trial date	01 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to provide long-term safety, efficacy, pharmacokinetics (PK), and immunogenicity data on BI 695501 administered via pre-filled syringe in patients with rheumatoid arthritis (RA) who have completed Trial 1297.2 (NCT02137226).

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2016
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	Bulgaria: 52
Country: Number of subjects enrolled	Chile: 27
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Poland: 139
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Serbia: 29
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Ukraine: 94
Country: Number of subjects enrolled	United States: 66
Worldwide total number of subjects	479
EEA total number of subjects	232

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)	392
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Open-label extension trial in adult patients with moderate to severely active rheumatoid arthritis (RA) who completed Trial NCT02137226 (1297.2), wished to participate in this extension trial and per Investigator's assessment could benefit from continuing to receive BI 695501 were included in this trial. Out of 479 screened patients 430 entered.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. The trial consisted of a Screening visit 14 days prior to Day 1, a 48-week treatment period and a 10-week safety follow up (SFU) period. The screening visit was the Week 48 visit in Trial 1297.2.

Period 1

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

Blinding implementation details:

No blinding of BI 695501 was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 695501 to BI 695501

Arm description:

Patients initially randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by subcutaneous (SC) injection every 2 weeks from Day 1 to Week 48.

Arm type	Experimental
Investigational medicinal product name	BI 695501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg/0.8 mL every 2 weeks from Day 1 to week 48.

Arm title	Humira® to Humira®

Arm description:

Patients initially randomized to Humira® in Period 1 and re-randomized to Humira® in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL Humira® in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Arm type	Active comparator
Investigational medicinal product name	Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg/0.8 mL every 2 weeks from Day 1 to Week 48.

Arm title	Humira® to BI 695501

Arm description:

Patients initially randomized to Humira® in Period 1 and re- randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Arm type	Active comparator
Investigational medicinal product name	Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg/0.8 mL every 2 weeks from Day 1 to Week 48.

Investigational medicinal product name	BI 695501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg/0.8 mL every 2 weeks from Day 1 to Week 48.

Number of subjects in period 1[1]	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501
Started	225	103	102
Completed	203	89	96
Not completed	22	14	6
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	10	3	3
Adverse event, non-fatal	6	7	2
Lost to follow-up	4	1	1
Lack of efficacy	1	1	-
Protocol deviation	-	2	-

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: Not all enrolled subjects were randomized in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	BI 695501 to BI 695501
Reporting group description:	
Patients initially randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by subcutaneous (SC) injection every 2 weeks from Day 1 to Week 48.	
Reporting group title	Humira® to Humira®
Reporting group description:	
Patients initially randomized to Humira® in Period 1 and re-randomized to Humira® in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL Humira® in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.	
Reporting group title	Humira® to BI 695501
Reporting group description:	
Patients initially randomized to Humira® in Period 1 and re- randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.	

Reporting group values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501
Number of subjects	225	103	102
Age categorical			
Units: Subjects			
Age Continuous			
Age of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: years			
arithmetic mean	53.8	51.7	54.6
standard deviation	± 11.87	± 11.21	± 9.90
Sex: Female, Male			
Gender distribution of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
Female	188	88	84
Male	37	15	18
Race (NIH/OMB)			
Race of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	7	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	0	2

White	215	100	100
More than one race	0	0	0
Unknown or Not Reported	0	1	0
Ethnicity (NIH/OMB)			
Ethnicity of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
Hispanic or Latino	23	8	10
Not Hispanic or Latino	199	94	92
Unknown or Not Reported	3	1	0

Reporting group values	Total		
Number of subjects	430		
Age categorical			
Units: Subjects			
Age Continuous			
Age of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Gender distribution of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
Female	360		
Male	70		
Race (NIH/OMB)			
Race of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	9		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	415		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB)			
Ethnicity of all patients included in the trial. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.			
Units: Subjects			
Hispanic or Latino	41		
Not Hispanic or Latino	385		

Unknown or Not Reported	4		

End points

End points reporting groups

Reporting group title	BI 695501 to BI 695501

Reporting group description:

Patients initially randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by subcutaneous (SC) injection every 2 weeks from Day 1 to Week 48.

Reporting group title	Humira® to Humira®

Reporting group description:

Patients initially randomized to Humira® in Period 1 and re-randomized to Humira® in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL Humira® in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Reporting group title	Humira® to BI 695501

Reporting group description:

Patients initially randomized to Humira® in Period 1 and re- randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Primary: Percentage of patients with drug-related Adverse Events (AEs) during the treatment phase

End point title	Percentage of patients with drug-related Adverse Events (AEs) during the treatment phase[1]

End point description:

The analysis of AEs was based on the concept of treatment-emergent AEs (TEAEs). Thus, all AEs with an onset after the first dose of trial drug up to a period of ten weeks after the last dose of trial drug were assigned to the current treatment for evaluation. Investigator assessed drug related AEs were AEs with a relationship to drug ticked "yes" according to the Investigator. Safety Analysis Set (SAF): All patients who received at least 1 dose during trial 1297.3. In the event of doubt as to whether a patient was treated or not, they were assumed to have been treated for the purposes of analysis, and thus included in the SAF. Patients were classified according to randomized/re-randomized treatments of Trial 1297.2.

End point type	Primary

End point timeframe:

From the first drug administration until 10 weeks after the last drug administration, up to 58 weeks.

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: The endpoint was only planned to be analyzed descriptively.

End point values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225[2]	103[3]	102[4]	
Units: Percentage of patients (%)				
number (not applicable)	21.3	20.4	17.6	

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Disease Activity Score in 28 joints (DAS 28) by Erythrocyte Sedimentation Rate (ESR) at week 48

End point title	Change from Baseline in Disease Activity Score in 28 joints (DAS 28) by Erythrocyte Sedimentation Rate (ESR) at week 48

End point description:

The DAS28 (ESR) score was derived using the following formulae: DAS28 (ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.014*(GH) + 0.7*ln(ESR) Where: • TJC28 = 28 joint count for tenderness • SJC28 = 28 joint count for swelling • GH = General Health component ofthe DAS (patient's global assessment of disease activity) • Ln (ESR) = natural logarithm of ESR. Last observation carried forward (LOCF) is the method used for handling missing components post baseline. Baseline for this trial was taken from the baseline of1297.2.

End point type	Secondary

End point timeframe:

Baseline and Week 48.

End point values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225[5]	103[6]	101[7]	
Units: Unit on scale				
arithmetic mean (standard deviation)	-3.01 (± 1.385)	-2.91 (± 1.323)	-2.98 (± 1.218)	

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients meeting American College of Rheumatology (ACR) 20% response criteria at Week 48

End point title	Percentage of patients meeting American College of Rheumatology (ACR) 20% response criteria at Week 48

End point description:

The percentage of patients meeting the ACR20 response criteria was assessed. A patient had an ACR20 response if all of the following occurred: A ≥ 20 % improvement in the swollen joint count (66 joints), A ≥ 20 % improvement in the tender joint count (68 joints), A ≥ 20 % improvement in at least three of the following assessments: Patient's assessment of pain, Patient's global assessment of disease activity (equivalent to the General Health component of the Disease Activity Score ([DAS]), Physician's global assessment of disease activity, Patient's assessment of physical function, as measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI) Acute phase reactant (C-reactive protein [CRP]).

End point type	Secondary

End point timeframe:

Week 48.

End point values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225[8]	103[9]	101[10]	
Units: Percentage of patients (%)				
number (not applicable)	76.9	76.7	73.3	

Notes:

[8] - FAS (NRI)

[9] - FAS (NRI)

[10] - FAS (NRI)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients who meet the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) definition of remission at Week 48

End point title	Percentage of patients who meet the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) definition of remission at Week 48

End point description:

The ACR/EULAR remission criteria were based on a Boolean definition. At any time point, the patient must have satisfied all of the following: • Tender joint count (TJC) ≤ 1 • Swollen joint count (SJC) ≤ 1 • C-reactive protein (CRP) ≤ 1 milligram/decilitre (mg/dL) • Patient global assessment of disease activity ≤ 10 (on a 0 to 100 scale). For TJC and SJC, use of a 28-joint count may have missed actively involved joints, particularly in the feet and ankles. It was preferable to include the feet and ankles when evaluating remission.

End point type	Secondary

End point timeframe:

Week 48.

End point values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225[11]	103[12]	101[13]	
Units: Percentage of patients (%)				
number (not applicable)	8.4	9.7	6.9	

Notes:

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with European League Against Rheumatism (EULAR) response (good response, moderate response, or no response) at Week 48

End point title	Percentage of patients with European League Against Rheumatism (EULAR) response (good response, moderate response, or no response) at Week 48

End point description:

Percentage of patients with European League Against Rheumatism (EULAR) response (good response, moderate response, or no response) were calculated at Week 48 (w48) for assessment of this outcome measure. No response: If improvement in DAS28 (ESR) at w48 <=0.6, or if DAS28(ESR) at w48 >5.1 and improvement is in range >0.6 to <1.2. Moderate response: If DAS28(ESR) at w48 <=5.1 and improvement is in range >0.6 to <1.2, or, DAS28(ESR) at w48 >3.2 and improvement is in range >=1.2. Good response: If DAS28(ESR) at w48 <=3.2 and improvement >=1.2.

End point type	Secondary

End point timeframe:

Week 48.

End point values	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	225[14]	103[15]	101[16]	
Units: Percentage of patients (%)				
number (not applicable)				
Good Response|	37.8	37.9	41.6	
Moderate Response|	49.8	54.4	51.5	
No Response|	9.3	5.8	3.0	

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 10 weeks after the last drug administration, up to 58 weeks.

Adverse event reporting additional description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. SAF was used for AE assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	BI 695501 to BI 695501

Reporting group description:

Patients initially randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by subcutaneous (SC) injection every 2 weeks from Day 1 to Week 48.

Reporting group title	Humira® to Humira®

Reporting group description:

Patients initially randomized to Humira® in Period 1 and re-randomized to Humira® in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL Humira® in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Reporting group title	Humira® to BI 695501

Reporting group description:

Patients initially randomized to Humira® in Period 1 and re- randomized to BI 695501 in Period 2 of the 1297.2 trial. Each patient received 40 mg/0.8 mL Humira® in period 1 and 40 mg/0.8 mL BI 695501 in period 2. The respective treatment was administered by SC injection every 2 weeks from Day 1 to Week 48.

Serious adverse events	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 225 (6.22%)	8 / 103 (7.77%)	4 / 102 (3.92%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign soft tissue neoplasm			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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
Ovarian cancer			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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
Haematoma			
subjects affected / exposed	0 / 225 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
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			
Cardiopulmonary failure			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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
Ileus paralytic			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Umbilical hernia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine polyp			
subjects affected / exposed	0 / 225 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Interstitial lung disease			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 225 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 225 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	0 / 225 (0.00%)	0 / 103 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Otitis media			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 225 (1.78%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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
Pyelonephritis chronic			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 103 (0.00%)	0 / 102 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 103 (0.97%)	0 / 102 (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

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

Non-serious adverse events	BI 695501 to BI 695501	Humira® to Humira®	Humira® to BI 695501
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 225 (4.00%)	6 / 103 (5.83%)	2 / 102 (1.96%)
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 225 (4.00%)	6 / 103 (5.83%)	2 / 102 (1.96%)
occurrences (all)	10	7	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2016	The details of the Trial Clinical Monitor were updated. The permitted visit window for the Screening visit was changed on the trial flowchart from ± 1 day to ± 3 days to align with Trial 1297.2. Footnotes in the trial flow chart were updated to specify that Visual analogue scale (VAS) assessments and completion of the Health Assessment Questionnaire – Disability Index (HAQ-DI) and 36-item Short Form Health Survey version 2 (SF-36 v2) questionnaires must be done prior to any visit procedures to avoid bias and that questionnaires completed for Trial 1297.2 would be used as baseline for Trial 1297.3. Footnotes in the trial flow chart were updated to specify that 2 consecutive Electrocardiogram (ECG) recordings needed to be taken. The requirement for patients with major protocol deviations in Trial 1297.2 was removed. Patients with major protocol deviations related to safety would still be excluded from Trial 1297.3 based on other specific exclusion criteria. Text was corrected regarding training of the independent joint assessor and for storage of Pharmacokinetic (PK) samples was revised in accordance with local regulation. The wording of information for storage of Anti-drug antibody (ADA) samples was revised as for the PK samples. Patient incidence was corrected from 100 patient-years to 1000 patient-years. References to off-treatment efficacy assessments were removed, as no off-treatment efficacy data was to be collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported