Clinical trial results:
Efficacy, safety, and immunogenicity of BI 695501 versus adalimumab in patients with active rheumatoid arthritis: a randomized, double-blind, parallel arm, multiple dose, active comparator trial.

Summary

EudraCT number	2012-002945-40
Trial protocol	DE HU EE ES BG
Global end of trial date	18 October 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	1297.2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02137226
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	01 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2016
Global end of trial reached?	Yes
Global end of trial date	18 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to establish equivalence in efficacy between BI 695501 and US licensed Humira® in patients with active rheumatoid arthritis (RA) based on a statistical comparison of the proportion of patients meeting the American College of Rheumatology 20% response criteria (ACR20) at Week 12 and at Week 24 between BI 695501 and US licensed Humira.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Other medication considered necessary for the patient's safety (e.g. as a result of an adverse event [AE]) was permitted at the Investigator's discretion.

Background therapy:

Each patient was to receive 40 mg of trial drug every 2 weeks by SC injection. Regardless of the treatment group they were allocated to, patients were to continue to take their regular methotrexate (MTX) therapy (15 to 25 milligram (mg) / week at a stable dose) and a stable weekly dose of adequate folic acid (at least 5 mg per week or as per local practice) or folinic acid (at least 1 mg per week or as per local practice) from their usual source.

Evidence for comparator: -

Actual start date of recruitment	04 February 2015
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: 86
Country: Number of subjects enrolled	Chile: 79
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Estonia: 22
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 201
Country: Number of subjects enrolled	Russian Federation: 41
Country: Number of subjects enrolled	Serbia: 40
Country: Number of subjects enrolled	Thailand: 6

Country: Number of subjects enrolled	Ukraine: 129
Country: Number of subjects enrolled	United States: 259
Worldwide total number of subjects	940
EEA total number of subjects	374

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)	735
From 65 to 84 years	205
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A randomized, double-blind, parallel arm, multiple dose, active comparator trial to assess efficacy, safety and immunogenicity of BI 695501 versus adalimumab in patients with active rheumatoid arthritis. Patient received background methotrexate (MTX) treatment.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist site which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Period 1 (Initial randomization)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 695501

Arm description:

Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 solution for injection, administered by subcutaneous (SC) injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).

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

Dosage and administration details:

Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 solution for injection, administered by subcutaneous (SC) injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1)

Arm title	US-licensed Humira®

Arm description:

Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).

Arm type	Active comparator
Investigational medicinal product name	BI 695501
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1)

Number of subjects in period 1[1]	BI 695501	US-licensed Humira®
Started	324	321
Completed	304	305
Not completed	20	16
Consent withdrawn by subject	11	5
Physician decision	1	3
Adverse event, non-fatal	3	3
Other Reason	1	3
Lost to follow-up	3	2
Lack of efficacy	1	-

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: Baseline characteristics are based on the patients who were randomized after successfully completing the screening period and received at least one of the trial medication.

Period 2

Period 2 title	Period 2 (Re - randomization)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

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. Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

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

Dosage and administration details:

Patients initially randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2. Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Arm title	US-licensed Humira® to US-licensed Humira®

Arm description:

Patients initially randomized to US-licensed Humira® in Period 1 and re-randomized to US-licensed Humira® in Period 2. Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Arm type	Active comparator

Investigational medicinal product name	US-licensed Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients initially randomized to US-licensed Humira® in Period 1 and re-randomized to US-licensed Humira® in Period 2. Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Arm title	US-licensed Humira® to BI 695501

Arm description:

Patients initially randomized to US-licensed Humira® in Period 1 and re-randomized to BI 695501 in Period 2. Each patient received 40 mg/0.8 mL US-licenced Humira® in period 1 and 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

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

Dosage and administration details:

Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Investigational medicinal product name	US-licensed Humira®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each patient received 40 mg/0.8 mL US-licenced Humira® in period 1 administered by SC injection every 2 weeks from Week 24 to Week 48.

Number of subjects in period 2[2]	BI 695501 to BI 695501	US-licensed Humira® to US-licensed Humira®	US-licensed Humira® to BI 695501
Started	298	148	147
Completed	281	140	138
Not completed	17	8	9
Consent withdrawn by subject	8	5	4
Physician decision	-	1	-
Adverse event, non-fatal	3	1	4
Other Reason	1	1	1
Lost to follow-up	3	-	-
Lack of efficacy	2	-	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 645 patients were initially randomized and 609 completed the initial randomization phase (Period 1). Out of which 593 patients were re-randomized and 559 completed the re-randomization phase (Period 2) .

Baseline characteristics

Reporting groups	
Reporting group title	BI 695501
Reporting group description:	
Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 solution for injection, administered by subcutaneous (SC) injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).	
Reporting group title	US-licensed Humira®
Reporting group description:	
Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).	

Reporting group values	BI 695501	US-licensed Humira®	Total
Number of subjects	324	321	645
Age categorical			
Safety Analysis Set (SAF): The SAF contained all patients who received at least one dose of trial drug.			
Units: Subjects			
Age Continuous			
Safety Analysis Set (SAF): The SAF contained all patients who received at least one dose of trial drug.			
Units: years			
arithmetic mean	53.7	53.6	
standard deviation	± 12.04	± 11.32	-
Gender, Male/Female			
Safety Analysis Set (SAF): The SAF contained all patients who received at least one dose of trial drug.			
Units: Subjects			
Female	267	269	536
Male	57	52	109

End points

End points reporting groups

Reporting group title	BI 695501

Reporting group description:

Each patient received 40 milligram (mg)/0.8 millilitre (mL) BI 695501 solution for injection, administered by subcutaneous (SC) injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).

Reporting group title	US-licensed Humira®

Reporting group description:

Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks up to and including the first 22 weeks of treatment (Period 1).

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. Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Reporting group title	US-licensed Humira® to US-licensed Humira®

Reporting group description:

Patients initially randomized to US-licensed Humira® in Period 1 and re-randomized to US-licensed Humira® in Period 2. Each patient received 40 mg/0.8 mL US-licenced Humira® solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Reporting group title	US-licensed Humira® to BI 695501

Reporting group description:

Patients initially randomized to US-licensed Humira® in Period 1 and re-randomized to BI 695501 in Period 2. Each patient received 40 mg/0.8 mL US-licenced Humira® in period 1 and 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks from Week 24 to Week 48.

Subject analysis set title	BI 695501 continuously
Subject analysis set type	Full analysis

Subject analysis set description:

BI 695501 continuously comprised all patients randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 (or not re randomized at Week 24). This group represents all patients who were to receive BI 695501 from Day 1 to Week 48. Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks.

Subject analysis set title	US-licensed Humira® continuously
Subject analysis set type	Full analysis

Subject analysis set description:

Humira® US continuously comprised all patients randomized to US-licensed Humira® in Period 1 and re-randomized to US-licensed Humira® in Period 2 or not re randomized at Week 24 (e.g. patients who discontinued treatment prior to Week 24). This group represents all patients who were to receive US-licensed Humira® from Day 1 to Week 48. Each patient received 40 mg/0.8 mL US-licensed Humira® solution for injection, administered by SC injection every 2 weeks.

Primary: The proportion of patients meeting the American College of Rheumatology 20% (ACR20) response criteria at week 12

End point title	The proportion of patients meeting the American College of Rheumatology 20% (ACR20) response criteria at week 12

End point description:

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]). Full Analysis Set (Patients with at least one dose of trial drug and had all relevant efficacy measures). Patients who discontinued treatment prior to the time-point had their binary response imputed as non-responder, a method commonly known as non-responder imputation. For truly missing data at the component level, multiple imputations were used.

End point type	Primary

End point timeframe:

Week 12

End point values	BI 695501	US-licensed Humira®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321[1]	318[2]		
Units: Percentage of Patients				
number (not applicable)	67	61.1		

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The week 12 confidence interval for the estimated difference in proportion is produced using the cumulative distribution function method of Reeve

Comparison groups	BI 695501 v US-licensed Humira®
Number of subjects included in analysis	639
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Regression, Logistic
Parameter estimate	Difference in proportions
Point estimate	5.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.9
upper limit	12.7

Notes:

[3] - The 90% Confidence Interval (CI) for ACR20 at Week 12, rounded to 1 decimal place, had to be entirely contained in the predefined equivalence region [-12.0%, 15.0%]. Results from logistic regression model adjusted for treatment, prior exposure to a biologic agent (yes / no), Baseline DAS28 (ESR). Difference in ACR20 Response Rate (BI695501 – Humira, %) is presented.

Primary: The proportion of patients meeting ACR20 response criteria at Week 24

End point title	The proportion of patients meeting ACR20 response criteria at Week 24

End point description:

ACR20 at Week 12 and Week 24 are standard outcome criteria that are widely accepted for regulatory purposes to demonstrate efficacy in treating the signs and symptoms of Rheumatoid arthritis (RA). The proportion of patients meeting the ACR20 response criteria was assessed at Week 12 and Week 24 to provide a robust comparison with US-licensed Humira® data. 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	Primary

End point timeframe:

Week 24

End point values	BI 695501	US-licensed Humira®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321[4]	318[5]		
Units: Percentage of Patients				
number (not applicable)	69	64.5		

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The week 24 confidence interval for the estimated difference in proportion is produced using the cumulative distribution function method of Reeve

Comparison groups	BI 695501 v US-licensed Humira®
Number of subjects included in analysis	639
Analysis specification	Pre-specified
Analysis type	other[6]
Method	Regression, Logistic
Parameter estimate	Difference in proportions
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	12.5

Notes:

[6] - The 95% Confidence Interval (CI) for ACR20 at Week 24, rounded to 1 decimal place, had to be entirely contained in the predefined equivalence region [-15.0%;+15.0%]. Results from logistic regression model adjusted for treatment, prior exposure to a biologic agent (yes / no), Baseline DAS28 (ESR). Difference in ACR20 Response Rate (BI695501 – Humira, %) is presented.

Secondary: Change from baseline in Disease Activity Score 28 (DAS28) (Erythrocyte sedimentation rate [ESR]) at Week 12 and Week 24

End point title	Change from baseline in Disease Activity Score 28 (DAS28) (Erythrocyte sedimentation rate [ESR]) at Week 12 and Week 24

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 • Ln (ESR) = natural logarithm of ESR • GH = General Health component of the DAS (patient's global assessment of disease activity). N is mean number of subjects in the analysis set with DAS28(ESR) results computable across the multiply imputed data sets. Patients who discontinued treatment prior to the time-point had their binary response imputed as non-responder, a method commonly known as non-responder imputation. For truly missing data at the component level, multiple imputation was used. The Full Analysis Set contained all enrolled patients who were randomized to trial drug and who received at least one dose of trial drug and had all efficacy measures relevant for the co-primary efficacy endpoints measured at baseline and at least once post- baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 24

End point values	BI 695501	US-licensed Humira®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321[7]	318[8]		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Week 12 (N= 319.6, 317.1)	-2.1 (-2.28 to -2.01)	-2 (-2.18 to -1.91)		
Week 24 (N=313.9, 315.1)	-2.4 (-2.51 to -2.21)	-2.4 (-2.54 to -2.24)		

Notes:

[7] - Full Analysis Set

[8] - Full Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Results based on DAS28 (ESR) mean changes from Baseline after 12 weeks of treatment = overall mean + treatment group + Baseline DAS28 (ESR) + prior exposure to a biologic agent + random error.

Comparison groups	BI 695501 v US-licensed Humira®
Number of subjects included in analysis	639
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.25
upper limit	0.05

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Results based on DAS28 (ESR) mean changes from Baseline after 24 weeks of treatment = overall mean + treatment group + Baseline DAS28 (ESR) + prior exposure to a biologic agent + random error.

Comparison groups	BI 695501 v US-licensed Humira®
Number of subjects included in analysis	639
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.23

Secondary: The proportion of patients with Investigator-assessed drug-related adverse events (AEs) during the treatment phase

End point title	The proportion of patients with Investigator-assessed drug-related adverse events (AEs) during the treatment phase

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. Overall results are presented from Day 1 up to Week 58 and are based on the initial randomization groups. The comparison therefore focuses on patients who received BI 695501 continuously versus patients who received Humira® continuously for the long term assessment of safety. One patient was initially treated with Humira and discontinued prior to Week 24. This patient was mistakenly re randomized to BI 695501 but not treated. For SAF this was counted in Humira not re-randomized group (as treated), and for other analysis sets, this patient was counted in the Humira to BI 695501 group (as randomized).

End point type	Secondary

End point timeframe:

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

End point values	BI 695501 continuously	US-licensed Humira® continuously		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	324[9]	175[10]		
Units: Percentage of Patients				
number (not applicable)	19.1	22.9		

Notes:

[9] - Safety Analysis Set

[10] - Safety Analysis Set

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:

Treatment-emergent adverse events are defined as adverse events that started or worsened on or after the first dose of study medication and prior to the last date of study medication plus 10 weeks (70 days) inclusive. Data is reported from Day 1 to the end of Period 2 (Week 58).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	US-licensed Humira® continuously

Reporting group description:

Humira® US continuously comprised all patients randomized to US-licensed Humira® in Period 1 and rerandomized to US-licensed Humira® in Period 2 or not re randomized at Week 24 (e.g. patients who discontinued treatment prior to Week 24). This group represents all patients who were to receive US-licensed Humira® from Day 1 to Week 48. Each patient received 40 mg/0.8 mL US-licensed Humira® solution for injection, administered by SC injection every 2 weeks.

Reporting group title	BI 695501

Reporting group description:

BI 695501 continuously comprised all patients randomized to BI 695501 in Period 1 and re-randomized to BI 695501 in Period 2 (or not re randomized at Week 24). This group represents all patients who were to receive BI 695501 from Day 1 to Week 48. Each patient received 40 mg/0.8 mL BI 695501 solution for injection, administered by SC injection every 2 weeks.

Serious adverse events	US-licensed Humira® continuously	BI 695501	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 174 (9.77%)	18 / 324 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostatic adenoma			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
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			
Interstitial lung disease			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rib fracture			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive cardiomyopathy			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
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			
Intervertebral disc disorder			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint destruction			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
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	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 174 (0.00%)	1 / 324 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 174 (1.72%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	2 / 174 (1.15%)	0 / 324 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	US-licensed Humira® continuously	BI 695501	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 174 (13.79%)	35 / 324 (10.80%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 174 (9.77%)	19 / 324 (5.86%)	
occurrences (all)	19	24	
Upper respiratory tract infection			
subjects affected / exposed	9 / 174 (5.17%)	17 / 324 (5.25%)	
occurrences (all)	9	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2014	Amendment 1: The endpoint 'number of patients with injection site pain' was removed from other endpoints as this was a safety endpoint. The wording 'EU-sourced Humira' was deleted from the description of the single dose PK study in cynomolgus monkeys as this study was not using EU-sourced Humira. Screening period was revised to 46 days and a pre randomization phase of up to ten days was added. It was clarified that the process for randomization and pre-randomization was dependent on site and country. It was clarified that patients were to be randomly assigned to trial drug according to both the randomization ratio and the stratification factors and that the same process was to be used for both the initial randomization and for re randomization. The requirement for patients with a history of hypersensitivity to adalimumab to be excluded from the trial was removed because patients who had received Humira before were not eligible, regardless of whether they had developed an immune reaction. It was clarified that the PPD or IGRA test could be performed at Week 48 for TB assessment; samples for the TB test was updated from 1 to 2 and blood volumes were revised accordingly. Only unblinded personnel were responsible for ensuring drug accountability and compliance; a unique drug number was to be assigned for each drug administration; syringes were not pre prepared but were provided to the sites pre filled; data for primary analysis were to be unblinded only for the team members involved in the primary analysis as well as PPK analysis. New template text was added for the definitions and reporting of cancers and protocol specified AESIs and reporting of AE/SAEs. In the statistical methods, text stating 'if a patient misses an entire visit the missing data will not be imputed' was deleted and updated to include 'Baseline' to clarify the process for handling of missing data. The power was updated to correct the calculations for DAS28 to reflect the power for 2 sided tests.
04 November 2014	Amendment 2: The primary objective updated to replace the co-primary endpoint of 'change in DAS28-ESR at 24 weeks compared to baseline' with 'proportion of patients meeting ACR20 response rate at Week 24'. Primary, secondary and other endpoints were updated based on the changes to the objectives. Sample size was increased to 650 patients to take into account the updated margins resulting from the change in primary endpoints. Safety endpoints were updated to state 'the proportion' instead of 'number and proportion', as only 1 item should be measured in an endpoint. The endpoint relating to injection site pain was deleted from the safety endpoints; this assessment was not deemed to provide relevant information for the trial as all injection site reactions were to be captured as AEs. A self administration arm was added to collect patient data on real life experience of self injection; the secondary and exploratory objectives were updated accordingly with a reference to this new arm. Injection-related endpoints were added to the 'other' endpoints category to allow assessment of self administration. Patients who discontinued the trial early were to be followed for efficacy until Week 48. Only qualified patients were to be offered participation in the OLE trial, not all patients. AEs were to be reported until the last per protocol visit. Patients who discontinued early were required to be followed up until Week 58. The hypotheses for the equivalence test, and the associated statistical margins, were updated to reflect the revised primary objective and endpoints. Secondary analysis was updated to include the new endpoints of the mean changes from baseline in DAS28-ESR after 12 weeks and was based on the FAS and used the LOCF method for missing values. Data reporting was amended to clarify that all efficacy data were to be reported at 24 weeks in a CTR and that a follow up analysis was to be conducted when all data were available and would be reported in follow up CTR.

20 February 2015	Amendment 3: It was implemented prior to IRB approval as the changes involved only logistical or administrative aspects. This amendment was implemented after the start of patient enrollment. Based on FDA feedback, the following changes were made throughout the CTP: The term US-sourced Humira was replaced by US-licensed Humira. References to Humira or adalimumab were updated to US-licensed Humira and/or EU approved Humira, as applicable. The term adalimumab was used for general mode of action descriptions of the molecule. The synopsis and trial flow chart were updated in line with the above mentioned changes, as appropriate.
27 April 2015	Amendment 4: Based on feedback from the FDA the following changes were implemented: Removal of the self administration arm. This was based on FDA feedback that self administration data from the use of pre filled syringes was not required and could have potentially compromised the blinding of the trial. The process of trial drug administration was changed such that the trial personnel responsible for administration were to be blinded. It was clarified that every effort should be made to follow up patients who discontinued trial drug for efficacy. The description of the analysis of the co primary endpoint of ACR20 at Week 12 was updated to state the use of 90% CIs and an equivalence margin of ± 12%. Additional safety ECG monitoring was implemented at Weeks 4, 12, 24, 40, 48, and 58. The criteria for withdrawal from the trial, discontinuation from trial drug, and the requirements for follow up of patients who discontinued treatment were clarified. The definitions and processes of AE collection and reporting were clarified; pregnancy reporting requirements were expanded to include female partners of male patients; aminotransferase was added as a parameter for identifying hepatic injury.
05 January 2016	Amendment 5: It was specified that the Week 48 efficacy endpoints would not be analyzed as part of the primary analysis of efficacy and safety in the current Week 32 CTR as not all Week 48 ACR20 data would be available at the data cut off for the primary analysis. The margins for the Week 12 primary efficacy assessment were updated from [-12%; 12%] to [-12%; 15%]. This slightly higher upper bound (+15%) allowed for variations in the imputation techniques and response rates used in the calculation of the margins and was agreed to by the FDA. The -12% lower bound was maintained in case the response rate for BI 695501 was lower than that for US-licensed Humira. The fixed categorical effect 'region' was removed from the primary efficacy endpoint models in order to prevent any potential issues due to sparse data from a region. The primary analysis cut off was changed from Week 24 to Week 32 to allow for an early evaluation of the initial 8 weeks of safety and immunogenicity data following transition for those patients who switched treatments at Week 24. Exclusion criterion 2 was updated to include 'per Investigator discretion' for consistency with the rest of the CTP. It was clarified that protocol deviations would be handled on a case by case basis; the term 'severe' in relation to protocol deviations was removed accordingly. It was clarified that the primary efficacy endpoint analysis would use two separate logistic regression models to address FDA feedback. The missing data imputation method for the primary and secondary analyses was changed from LOCF to MI to address FDA feedback.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported