Clinical trial results:
The VOLTAIRE-X trial looks at the effect of switching between Humira® and BI 695501 in patients with plaque psoriasis.

Summary

EudraCT number	2016-002254-20
Trial protocol	LV HU DE PL
Global end of trial date	18 April 2019

Results information

Result version number	v3 (current)
This version publication date	24 September 2021
First version publication date	01 May 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1297-0009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03210259
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	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 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	02 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2019
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 assess the pharmacokinetic (PK) similarity between patients receiving United States (US)-licensed Humira continuously versus those who switched between BI 695501 and US-licensed Humira in patients with moderate to severe chronic plaque psoriasis.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be 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. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2017
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	Germany: 18
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Latvia: 34
Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 81
Worldwide total number of subjects	259
EEA total number of subjects	152

Notes:

Subjects enrolled per age group

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

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	236
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 58-week, multiple-dose, active comparator trial of BI 695501 and US-licensed Humira in patients with moderate to severe chronic plaque psoriasis. The trial was conducted at 49 trial centers in 7 countries (Germany, Hungary, Latvia, Poland, Russian Federation, Ukraine, and the United States [US]).

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. The trial consisted of a single-arm run-in period of 14 weeks for all patients, followed by a randomized, double-blind, 2-arm period of 34 weeks. The total treatment period was 48 weeks followed by 10 weeks of safety follow up (SFU).

Period 1

Period 1 title	Period 1: Run-In Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-In Period (Humira)

Arm description:

All patients received US-licensed Humira during the run-in period (Period 1). Patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. Trial medication was administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes containing 40 mg of adalimumab per 0.8 milliliter (mL).

Arm type	Active comparator
Investigational medicinal product name	US-licensed Humira
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

US-licensed Humira was provided in single-use pre-filled syringes (PFS) containing 40 milligrams (mg) of adalimumab per 0.8 milliliter (mL). 2 syringes (80 mg) were used at Day 1 (Week 1) as loading dose. 40 mg was used every other week from Week 2 to Week 12.

Number of subjects in period 1	Run-In Period (Humira)
Started	259
Completed	238
Not completed	21
Adverse event, serious fatal	1
Missed study visits	3
Consent withdrawn by subject	8
Adverse event, non-fatal	1
Lost to follow-up	3

Lack of efficacy	5

Period 2

Period 2 title	Period 2: Post-Randomization Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Switching Arm

Arm description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the switching arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg BI 695501 at Week 14 and Week 16 (2 injections), followed by 40 mg US-licensed Humira at Week 18 and Week 20 (2 injections), and subsequently 40 mg BI 695501 every other week from Week 22 to Week 48 (14 injections). Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab or BI 695501 per 0.8 milliliter (mL).

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

Dosage and administration details:

BI 695501 was provided in single-use PFS containing 40 mg of BI 695501 per 0.8 mL. One syringe was used per injection. Patients received 40 mg of BI 695501 at Week 14 and Week 16 (2 injections), and every other week from Week 22 to Week 48 (14 injections).

Investigational medicinal product name	US-licensed Humira
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

US-licensed Humira was provided in single-use PFS containing 40 mg of adalimumab per 0.8 mL. One syringe was used per injection. Patients received 40 mg US-licensed Humira at Week 18 and Week 20 (2 injections).

Arm title	Continuous Humira

Arm description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the continuous Humira arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 mg US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week

from Week 2 to Week 12. During Period 2, patients received 40 mg US-licensed Humira every other week from Week 14 to Week 48 (18 injections). Trial medication were administered by s.c. injection providing in single-use PFS containing 40 mg of adalimumab per 0.8 mL.

Arm type	Active comparator
Investigational medicinal product name	US-licensed Humira
Investigational medicinal product code	
Other name	Adalimumab
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

US-licensed Humira was provided in single-use PFS containing 40 mg of adalimumab per 0.8 mL. One syringe was used per injection. Patients received 40 mg US-licensed Humira every other week from Week 14 to Week 48.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are reported based on the randomised set.

Number of subjects in period 2[2]	Switching Arm	Continuous Humira
Started	118	120
Completed	107	91
Not completed	11	29
Missed study visits	1	2
Consent withdrawn by subject	5	17
Physician decision	-	1
Adverse event, non-fatal	1	1
Pregnancy	1	-
Lost to follow-up	3	8

Notes:

[2] - 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: All patients received US-licensed Humira during the run-in period followed by randomized, parallel-arm period.

Baseline characteristics

Reporting groups	
Reporting group title	Switching Arm

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the switching arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg BI 695501 at Week 14 and Week 16 (2 injections), followed by 40 mg US-licensed Humira at Week 18 and Week 20 (2 injections), and subsequently 40 mg BI 695501 every other week from Week 22 to Week 48 (14 injections). Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab or BI 695501 per 0.8 milliliter (mL).

Reporting group title	Continuous Humira

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the continuous Humira arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 mg US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg US-licensed Humira every other week from Week 14 to Week 48 (18 injections). Trial medication were administered by s.c. injection providing in single-use PFS containing 40 mg of adalimumab per 0.8 mL.

Reporting group values	Switching Arm	Continuous Humira	Total
Number of subjects	118	120	238
Age categorical			
The Treated Set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	104	112	216
From 65-84 years	14	8	22
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	46.1	43.7	
standard deviation	± 13.95	± 13.69	-
Sex: Female, Male			
The Treated Set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.			
Units:			
Female	37	44	81
Male	81	76	157
Ethnicity (NIH/OMB)			
The Treated Set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.			

Units: Subjects			
Hispanic or Latino	18	18	36
Not Hispanic or Latino	100	102	202
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
The Treated Set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	0	2
White	113	119	232
More than one race	0	0	0
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Run-In Period (Humira)

Reporting group description:

All patients received US-licensed Humira during the run-in period (Period 1). Patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. Trial medication was administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes containing 40 mg of adalimumab per 0.8 milliliter (mL).

Reporting group title	Switching Arm

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the switching arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg BI 695501 at Week 14 and Week 16 (2 injections), followed by 40 mg US-licensed Humira at Week 18 and Week 20 (2 injections), and subsequently 40 mg BI 695501 every other week from Week 22 to Week 48 (14 injections). Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab or BI 695501 per 0.8 milliliter (mL).

Reporting group title	Continuous Humira

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the continuous Humira arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 mg US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg US-licensed Humira every other week from Week 14 to Week 48 (18 injections). Trial medication were administered by s.c. injection providing in single-use PFS containing 40 mg of adalimumab per 0.8 mL.

Primary: Area Under the Plasma Concentration time Curve Over Dosing Interval of Week 30 to 32 (AUCτ, 30-32) for Adalimumab in plasma

End point title	Area Under the Plasma Concentration time Curve Over Dosing Interval of Week 30 to 32 (AUCτ, 30-32) for Adalimumab in plasma

End point description:

Area Under the Plasma Concentration Time Curve Over the 2 weeks Dosing Interval of Week 30 to 32 for Adalimumab in plasma. The PK Set (PKS) included all patients from the TS who provided at least 1 primary PK parameter that was not excluded due to a protocol violation relevant to the evaluation of PK.

End point type	Primary

End point timeframe:

Pre-dose at Week 30, at 72, 120, 168 and 240 hours after the Week 30 dosing, and pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	93		
Units: microgram * hours /milliliter				
arithmetic mean (standard deviation)	2040 (± 1420)	1980 (± 1600)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis was that the ratio of expected means for Switching vs. Continuous Humira is less than 80.00% or more than 125.00%. Equivalence was concluded if the confidence interval (CI) for the least square (LS) means ratio was included in the pre-defined equivalence range of 80.00% to 125.00%. The number 195 reflects the descriptive analysis of the endpoint values. The number of subjects contributing to the statistical analysis was 187.

Comparison groups	Switching Arm v Continuous Humira
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Least squares means ratio
Point estimate	105.19
Confidence interval	
level	90.2 %
sides	2-sided
lower limit	96.58
upper limit	114.64

Notes:

[1] - The least squares means were from ANCOVA. Ratio calculated with the switching arm as numerator and the continuous arm as the denominator.

Primary: Maximum Observed Concentration during the dosing interval Week 30-32 (Cmax, 30-32) for Adalimumab in plasma

End point title	Maximum Observed Concentration during the dosing interval Week 30-32 (Cmax, 30-32) for Adalimumab in plasma

End point description:

Maximum observed concentration during the 2 weeks dosing interval of Week 30-32 for Adalimumab in plasma. The PK Set (PKS) included all patients from the TS who provided at least 1 primary PK parameter that was not excluded due to a protocol violation relevant to the evaluation of PK.

End point type	Primary

End point timeframe:

Pre-dose at Week 30, at 72, 120, 168 and 240 hours after the Week 30 dosing, and pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	99		
Units: microgram /milliliter				
arithmetic mean (standard deviation)	7.13 (± 4.63)	7.14 (± 5.37)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis was that the ratio of expected means for Switching vs. Continuous Humira is less than 80.00% or more than 125.00%. Equivalence was concluded if the confidence interval (CI) for the least square (LS) means ratio was included in the pre-defined equivalence range of 80.00% to 125.00%. The number 203 reflects the descriptive analysis of the endpoint values. The number of subjects contributing to the statistical analysis was 197.

Comparison groups	Switching Arm v Continuous Humira
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Least squares means ratio
Point estimate	101.14
Confidence interval	
level	90.2 %
sides	2-sided
lower limit	93.26
upper limit	109.7

Notes:

[2] - The least squares means were from ANCOVA. Ratio calculated with the switching arm as numerator and the continuous arm as the denominator.

Secondary: Minimum Observed Concentration During the Dosing Interval of Week 30 to 32 (Cmin, 30-32) for Adalimumab in plasma

End point title	Minimum Observed Concentration During the Dosing Interval of Week 30 to 32 (Cmin, 30-32) for Adalimumab in plasma

End point description:

Minimum Observed Concentration During the 2 weeks Dosing Interval of Week 30 to 32 for Adalimumab in plasma. The PK Set (PKS) included all patients from the TS who provided at least 1 primary PK parameter that was not excluded due to a protocol violation relevant to the evaluation of PK.

End point type	Secondary

End point timeframe:

Pre-dose at Week 30, at 72, 120, 168 and 240 hours after the Week 30 dosing, and pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	98		
Units: micogram / milliliter				
arithmetic mean (standard deviation)	5.04 (± 3.89)	4.66 (± 4.19)		

Statistical analyses

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

No hypothesis was defined and no statistical test was performed. The number of subjects contributing to the statistical analysis was 195.

Comparison groups	Switching Arm v Continuous Humira
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Least squares mean ratio
Point estimate	107.31
Confidence interval	
level	90.2 %
sides	2-sided
lower limit	97.33
upper limit	118.43

Notes:

[3] - The least squares means were from ANCOVA. Ratio calculated with the switching arm as numerator and the continuous arm as the denominator.

Secondary: Time to Maximum Observed Concentration During the Dosing Interval of Week 30 to 32 (tmax, 30-32) for Adalimumab in plasma

End point title	Time to Maximum Observed Concentration During the Dosing Interval of Week 30 to 32 (tmax, 30-32) for Adalimumab in plasma

End point description:

Time to Maximum Observed Concentration During the Dosing Interval of Week 30 to 32 for Adalimumab in plasma. The PK Set (PKS) included all patients from the TS who provided at least 1 primary PK parameter that was not excluded due to a protocol violation relevant to the evaluation of PK.

End point type	Secondary

End point timeframe:

Pre-dose at Week 30, at 72, 120, 168 and 240 hours after the Week 30 dosing, and pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	99		
Units: hours				
median (full range (min-max))	72.7 (66.0 to 336)	72.3 (46.8 to 240)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With a 75% Reduction in Psoriasis Area and Severity Index (PASI75) Response at Week 32

End point title	Percentage of Patients With a 75% Reduction in Psoriasis Area and Severity Index (PASI75) Response at Week 32

End point description:

PASI is a measure of clinical efficacy for psoriasis medications via numeric scores for overall psoriasis disease state, with scores ranging from 0 to 72. It is a linear combination of percent (%) of surface area of affected skin and the severity of erythema, induration, and desquamation over four body regions (head, trunk, upper extremities and lower extremities). Higher PASI scores indicate more severe psoriasis. PASI is summarized as a dichotomous outcome based on achieving over an X% reduction from baseline (PASIX), where X is 50, 75, 90, and 100. Percentage of patients with a PASI75 response at Week 32 was reported. The Per-protocol Analysis Set (PPS) contained all patients from the TS who did not experience any important protocol violations relevant for efficacy. Missing data were imputed via non-responder imputation for patients who discontinued treatment early and multiple imputation (MI) for missing at random value. There were no cases where it was required to implement MI.

End point type	Secondary

End point timeframe:

At week 32

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	119		
Units: Percentage of patients				
number (not applicable)	84.75	78.99		

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

No hypothesis was tested. Risk difference was calculated as Switching arm minus Continuous Humira.

Comparison groups	Switching Arm v Continuous Humira
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	5.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.45
upper limit	13.96

Secondary: Percentage of Patients With a Static Physician's Global Assessment (sPGA) Score ≤ 1 (Clear or Almost Clear) at Week 32

End point title	Percentage of Patients With a Static Physician's Global Assessment (sPGA) Score ≤ 1 (Clear or Almost Clear) at Week 32

End point description:

The sPGA is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static", which refers to the patient's disease state at the time of the assessments, without comparison to any of the patient's previous disease states (dynamic), whether at baseline or at a previous visit. A lower score indicates less body coverage and a higher score indicates more severe disease (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe). Percentage of patients with a sPGA score of ≤ 1 (clear or almost clear) at Week 32 was reported. The PPS contained all patients from the TS who did not experience any important protocol violations relevant for efficacy. Missing data were imputed via non-responder imputation for patients who discontinued treatment early and multiple imputation (MI) for missing at random value. There were no cases where it was required to implement MI.

End point type	Secondary

End point timeframe:

At week 32

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	119		
Units: Percentage of patients				
number (not applicable)	70.34	64.71		

Statistical analyses

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

No hypothesis was tested. Risk difference was calculated as Switching arm minus Continuous Humira.

Comparison groups	Switching Arm v Continuous Humira
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	5.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.35
upper limit	15.62

Secondary: Number of Patients With Anti-drug Antibodies (ADA) to Adalimumab at Week 32

End point title	Number of Patients With Anti-drug Antibodies (ADA) to Adalimumab at Week 32

End point description:

Number of patients with a confirmed positive anti-drug antibody (ADA) response to Adalimumab (BI 695501 or Humira) at Week 32. A participant was considered "ADA positive" if the blank normalized signal in the ADA screening assay was equal to or above the study specific ADA screening cut point factor of 1.06 and the signal inhibition by drug in the ADA confirmatory assay was equal to or above the study specific ADA confirmatory cut points (11.4% for signal inhibition with Humira and 12.0% for signal inhibition with BI 695501).

Patients in the TS who had non-missing endpoints. The treated set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Participants				
Negative	11	6		
Positive	101	104		
Total reportable	112	110		
Not reportable	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Neutralizing Anti-drug Antibodies (nAb) to Adalimumab at Week 32

End point title	Number of Patients With Neutralizing Anti-drug Antibodies (nAb) to Adalimumab at Week 32

End point description:

Number of patients with a positive neutralizing anti-drug antibody (nAb) response to Adalimumab (BI 695501 or Humira) at Week 32. A participant was considered "nAb positive" if the blank normalized signal in the nAb screening assay was equal to or below the study specific nAb screening cut point factor of 0.836.

Patients in the TS who had non-missing endpoints. The treated set (TS) contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	112		
Units: Participants				
Negative	66	64		
Positive	46	46		
Total Reportable	112	110		
Not Reportable	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-drug antibody (ADA) titer of patients with ADA at Week 32

End point title	Anti-drug antibody (ADA) titer of patients with ADA at Week 32

End point description:

Anti-drug antibody (ADA) titer of patients with a confirmed positive ADA response to Adalimumab (BI 695501 or Humira) at Week 32. Analysis was on patients in the treated set (TS) with positive ADAs at week 32. The TS contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	104		
Units: Titer				
median (inter-quartile range (Q1-Q3))	64.0 (32.00 to 256.00)	128.0 (16.00 to 256.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralizing Anti-drug Antibody (nAb) titer of patients with nAb at Week 32

End point title	Neutralizing Anti-drug Antibody (nAb) titer of patients with nAb at Week 32

End point description:

Neutralizing anti-drug antibody (nAb) titer of patients with a positive nAb response to Adalimumab (BI 695501 or Humira) at Week 32. Analysis was on patients in the treated set (TS) with positive nAb at week 32. The TS contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected pre-dose at Week 32.

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Titer				
median (inter-quartile range (Q1-Q3))	2.0 (1.00 to 4.00)	2.0 (1.00 to 2.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Drug-related adverse events (AEs) During the Post-Randomization Period

End point title	Percentage of Patients With Drug-related adverse events (AEs) During the Post-Randomization Period

End point description:

Analysis of AEs focused on treatment-emergent adverse events (TEAEs) and is presented here for the post-randomization period (Week 14 to 58). For the post-randomization period analysis, TEAEs were defined as AEs that started or worsened on or after the first dose of trial post-randomization medication and prior to the last dose of trial post-randomization medication + 10 weeks. Endpoint was measured on treated set (TS) that contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period.

End point type	Secondary

End point timeframe:

From first dose of trial post-randomization medication until 10 weeks after last dose of trial post-randomization medication, up to 44 weeks

End point values	Switching Arm	Continuous Humira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	120		
Units: Percentage of patients				
number (not applicable)	11.9	18.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first post-randomized trial medication until 10 weeks after last dose, up to 44 weeks (Post-Randomization Period). From first dose of Humira and prior to the first dose of post-randomization medication+10 weeks, up to 24 weeks (Run-In Period).

Adverse event reporting additional description:

Safety analyses were performed based on the Treated Set (TS) and Run-in Treated Set (RTS). The TS contained all randomized patients who received at least 1 dose of trial medication administered in the post-randomization period. The RTS contained all enrolled patients treated with at least 1 dose of US-licensed Humira during the run-in period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Humira containing all RTS subjects (Run-In Period)

Reporting group description:

All patients received US-licensed Humira during the run-in period of 14 weeks (Period 1). Patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab per 0.8 milliliter (mL).

Reporting group title	Switching Arm (Post-Randomization Period)

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the switching arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg BI 695501 at Week 14 and Week 16 (2 injections), followed by 40 mg US-licensed Humira at Week 18 and Week 20 (2 injections), and subsequently 40 mg BI 695501 every other week from Week 22 to Week 48 (14 injections). Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab or BI 695501 per 0.8 milliliter (mL).

Reporting group title	Continuous Humira (Post-Randomization Period)

Reporting group description:

Patients initially received US-licensed Humira during the run-in period of 14 weeks (Period 1) and were then randomized to the continuous Humira arm for the randomized treatment period of 34 weeks (Period 2) followed by 10 weeks of safety follow-up. During Period 1, patients were administered with a loading dose of 80 milligram (mg) US-licensed Humira on Day 1 (Week 1), followed by 40 mg every other week from Week 2 to Week 12. During Period 2, patients received 40 mg US-licensed Humira every other week from Week 14 to Week 48 (18 injections).Trial medication were administered by subcutaneous (s.c.) injection providing in single-use pre-filled syringes (PFS) containing 40 mg of adalimumab per 0.8 milliliter (mL).

Serious adverse events	Humira containing all RTS subjects (Run-In Period)	Switching Arm (Post-Randomization Period)	Continuous Humira (Post-Randomization Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 259 (2.32%)	5 / 118 (4.24%)	4 / 120 (3.33%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Injury, poisoning and procedural complications			
Diffuse axonal injury			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Joint dislocation			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Ligament rupture			
subjects affected / exposed	0 / 259 (0.00%)	0 / 118 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 259 (0.00%)	0 / 118 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Sinus arrest			
subjects affected / exposed	0 / 259 (0.00%)	0 / 118 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Demyelination			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Microcytic anaemia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Pancreatitis acute			

subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	1 / 259 (0.39%)	0 / 118 (0.00%)	0 / 120 (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
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Influenza			
subjects affected / exposed	0 / 259 (0.00%)	1 / 118 (0.85%)	0 / 120 (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
Pneumonia chlamydial			
subjects affected / exposed	0 / 259 (0.00%)	0 / 118 (0.00%)	1 / 120 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Humira containing all RTS subjects (Run-In Period)	Switching Arm (Post-Randomization Period)	Continuous Humira (Post-Randomization Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 259 (9.27%)	17 / 118 (14.41%)	11 / 120 (9.17%)
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	10 / 259 (3.86%) 10	6 / 118 (5.08%) 7	6 / 120 (5.00%) 6
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	16 / 259 (6.18%) 20	11 / 118 (9.32%) 12	5 / 120 (4.17%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2017	Number of sites increased from 75 to 80; (administrative) corrections and updates to screening procedures, PK sampling procedures and specifications, and schedule of events; further PK endpoints added; change in bioanalytical lab.
18 April 2019	The actual date of the amendment was 25 Jul 2019. Based on a pre-defined blinded interim analysis, the primary statistical analysis method was adapted based on the discussion with USFDA after the global end of trial; The trial remained fully blinded; BLQ plasma concentrations were replaced by 1/2 LLOQ of the bioanalytical assay (except samples taken at Baseline Visit 2).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported