Clinical trial results:
BI 695501 versus Humira® in patients with active Crohn's disease: a randomized, double-blind, multicenter, parallel group, exploratory trial comparing efficacy, endoscopic improvement, safety, and immunogenicity

Summary

EudraCT number	2016-000612-14
Trial protocol	DE GB CZ GR HR
Global end of trial date	13 May 2019

Results information

Result version number	v2 (current)
This version publication date	25 December 2020
First version publication date	15 May 2020
Version creation reason	• New data added to full data set Addition of NCT Number in section Trial Information.

Trial information

Trial identification

Sponsor protocol code	1297.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02871635
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, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, 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	07 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2019
Global end of trial reached?	Yes
Global end of trial date	13 May 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 compare the clinical efficacy of BI 695501 with EU-approved Humira at Week 4 in patients with active Crohn’s disease.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be randomized 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2016
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	Belarus: 9
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Czechia: 51
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Croatia: 9
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Serbia: 19
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 34
Country: Number of subjects enrolled	United States: 77
Worldwide total number of subjects	365
EEA total number of subjects	127

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)	352
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an exploratory, randomized, 56-week, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and EU-approved Humira, with a 48-week treatment period and a 10-week follow-up period (starting after last dose of trial medication at Week 46) in patients with moderately to severely active Crohn's Disease (CD)

Pre-assignment

Screening details:

The trial consisted of a screening period of up to a maximum of 28 days, a 48-week treatment period consisting of an induction period from baseline to Week 4 and a maintenance period from Week 5 to Week 48, and a 10-week safety follow-up period (starting after last dose of trial medication at Week 46).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 695501

Arm description:

Patients randomized to BI 695501 received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders (Crohn's Disease Activity Index (CDAI) decrease of ≥70 compared to baseline), patients continued to receive BI 695501 every 2 weeks until the end of the treatment (EoT) period (Week 46). Patients were administered with a loading dose of 160 milligram (mg) BI 695501 on Day 1, followed by 80 mg BI 695501 2 weeks later (Day 15), and thereafter 40 mg BI 695501 every 2 weeks until Week 46. Trial medication was administered by subcutaneous (SC) injection.

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 sterile, preservative-free, non-pyrogenic, single-use pre-filled syringes (PFS) containing 40 mg of BI 695501 per 0.8 milliliter (mL). On Day 1, 4 PFS were used (total of 160 mg); on Day 15 (Week 2), 2 PFS were used (total of 80 mg); and thereafter (Week 4, then every 2 weeks until Week 46 if the patient was eligible to enter the maintenance phase, 1 PFS was used per injection.

Arm title	Humira EU

Arm description:

Patients randomized to EU-approved Humira received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders, patients continued to receive EU-approved Humira until Week 22 and then switched to receive BI 695501 every 2 weeks from Week 24 until the EoT period (Week 46). Patients were administered with a loading dose of 160 mg EU-approved Humira on Day 1, followed by 80 mg EU-approved Humira 2 weeks later (Day 15), and 40 mg EU-approved Humira every 2 weeks until Week 22. Patients were then switched to receive 40 mg BI 695501 every 2 weeks from Week 24 until Week 46. Trial medication was administered by SC injection.

Arm type	Active comparator

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

Dosage and administration details:

The EU-approved Humira was provided in sterile, preservative-free, non-pyrogenic, single use PFS containing 40 mg of adalimumab per 0.8 mL or 40 mg of adalimumab per 0.4 mL (old and new formulations, respectively, approved to be comparable). On Day 1, 4 PFS were used (total of 160 mg); on Day 15 (Week 2), 2 PFS were used (total of 80 mg); and thereafter (Week 4, then every 2 weeks until Week 22 if the patient was eligible to enter the maintenance phase), 1 PFS was used per injection.

Number of subjects in period 1[1]	BI 695501	Humira EU
Started	72	75
Completed	54	56
Not completed	18	19
Protocol deviation	3	1
Physician decision	1	1
Pregnancy	-	2
Secondary lack of efficacy	2	1
Adverse event, non-fatal	4	4
Primary lack of efficacy	4	4
Consent withdrawn by subject	3	4
Lost to follow-up	1	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: This table is based on the randomized set and not on the subjects enrolled

Baseline characteristics

Reporting groups	
Reporting group title	BI 695501

Reporting group description:

Patients randomized to BI 695501 received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders (Crohn's Disease Activity Index (CDAI) decrease of ≥70 compared to baseline), patients continued to receive BI 695501 every 2 weeks until the end of the treatment (EoT) period (Week 46). Patients were administered with a loading dose of 160 milligram (mg) BI 695501 on Day 1, followed by 80 mg BI 695501 2 weeks later (Day 15), and thereafter 40 mg BI 695501 every 2 weeks until Week 46. Trial medication was administered by subcutaneous (SC) injection.

Reporting group title	Humira EU

Reporting group description:

Patients randomized to EU-approved Humira received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders, patients continued to receive EU-approved Humira until Week 22 and then switched to receive BI 695501 every 2 weeks from Week 24 until the EoT period (Week 46). Patients were administered with a loading dose of 160 mg EU-approved Humira on Day 1, followed by 80 mg EU-approved Humira 2 weeks later (Day 15), and 40 mg EU-approved Humira every 2 weeks until Week 22. Patients were then switched to receive 40 mg BI 695501 every 2 weeks from Week 24 until Week 46. Trial medication was administered by SC injection.

Reporting group values	BI 695501	Humira EU	Total
Number of subjects	72	75	147
Age categorical			
The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication			
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)	68	74	142
From 65-84 years	4	1	5
85 years and over	0	0	0
Age Continuous			
The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication			
Units: years			
arithmetic mean	37.4	33.2	
standard deviation	± 13.44	± 11.52	-
Sex: Female, Male			
Units: Participants			
Female	33	31	64
Male	39	44	83
Race (NIH/OMB)			
The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication			
Units: Subjects			
American Indian or Alaska Native	0	0	0

Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	69	74	143
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Ethnicity (NIH/OMB)			
The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication			
Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	69	67	136
Unknown or Not Reported	2	8	10
Crohn’s Disease Activity Index score at baseline			
Crohn’s Disease Activity Index (CDAI) is a validated instrument to measure disease severity in Crohn’s disease. The CDAI is composed of 8 factors (Number of liquid stools, abdominal pain, general well being, extra-intestinal complications, antidiarrheal drugs, abdominal mass, hematocrit, body weight) the score is calculated by adding up the scores of the 8 factors after adjustment with a weighting factor. Higher CDAI scores indicating more active disease. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication			
Units: Score			
arithmetic mean	307.3	303.6	
standard deviation	± 76.69	± 64.39	-

End points

End points reporting groups

Reporting group title	BI 695501

Reporting group description:

Patients randomized to BI 695501 received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders (Crohn's Disease Activity Index (CDAI) decrease of ≥70 compared to baseline), patients continued to receive BI 695501 every 2 weeks until the end of the treatment (EoT) period (Week 46). Patients were administered with a loading dose of 160 milligram (mg) BI 695501 on Day 1, followed by 80 mg BI 695501 2 weeks later (Day 15), and thereafter 40 mg BI 695501 every 2 weeks until Week 46. Trial medication was administered by subcutaneous (SC) injection.

Reporting group title	Humira EU

Reporting group description:

Patients randomized to EU-approved Humira received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders, patients continued to receive EU-approved Humira until Week 22 and then switched to receive BI 695501 every 2 weeks from Week 24 until the EoT period (Week 46). Patients were administered with a loading dose of 160 mg EU-approved Humira on Day 1, followed by 80 mg EU-approved Humira 2 weeks later (Day 15), and 40 mg EU-approved Humira every 2 weeks until Week 22. Patients were then switched to receive 40 mg BI 695501 every 2 weeks from Week 24 until Week 46. Trial medication was administered by SC injection.

Primary: Percentage of Patients With a Clinical Response (CDAI Decrease of ≥70 Compared With Baseline) at Week 4

End point title	Percentage of Patients With a Clinical Response (CDAI Decrease of ≥70 Compared With Baseline) at Week 4

End point description:

The Crohn’s Disease Activity Index (CDAI) is a validated instrument to measure disease severity in Crohn’s Disease (CD). The CDAI score is a sum of the 8 factors (number of liquid stools, abdominal pain, general well-being, extra-intestinal complications, antidiarrheal drugs, abdominal mass, hematocrit and body weight) after adjustment with a weighting factor. Higher CDAI scores indicating more active disease. The CDAI decrease at Week 4 was assessed as the decrease relative to baseline measurement, patients with a decrease ≥70 were responders. Percentage=least squares means per treatment group back transformed using inverse logit function. Missing data were imputed according to non-responder imputation (NRI) and last observation carried forward (LOCF). The full analysis set (FAS) contained all randomized patients who received at least 1 dose of trial medication, and had all efficacy measures relevant for the CDAI, measured at baseline and at least once postbaseline.

End point type	Primary

End point timeframe:

Week 4

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	72		
Units: Percentage				
number (not applicable)	88.0	93.1		

Statistical analyses

Statistical analysis title	Estimate for relative risk
Statistical analysis description:	
Was analyzed using a log-linked binomial model, described as: response to treatment at Week 4 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)	
Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.945
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1.028

Statistical analysis title	Estimate for relative risk
Statistical analysis description:	
Was to be analyzed using a log-linked binomial model, described as: response to treatment at Week 4 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)	
Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.945
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.856
upper limit	1.044

Secondary: Percentage of Patients in Clinical Remission (CDAI <150) at Week 24

End point title	Percentage of Patients in Clinical Remission (CDAI <150) at Week 24

End point description:

The CDAI is a validated instrument to measure disease severity in CD. The CDAI score is a sum of the 8 factors (number of liquid stools, abdominal pain, general well-being, extra-intestinal complications, antidiarrheal drugs, abdominal mass, hematocrit and body weight) after adjustment with a weighting factor. Higher CDAI scores indicating more active disease. Patients with CDAI <150 at Week 24 were considered as clinical remission cases. Percentage=least squares means per treatment group back transformed using inverse logit function. Missing data were imputed according to NRI and LOCF. The full analysis set (FAS) contained all randomized patients who received at least 1 dose of trial medication, and had all efficacy measures relevant for the CDAI, measured at baseline and at least once postbaseline.

End point type	Secondary

End point timeframe:

at Week 24

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	72		
Units: Percentage				
number (not applicable)	68.6	76.2		

Statistical analyses

Statistical analysis title	Estimate for relative risk
Statistical analysis description:	
Was to be analyzed using a log-linked binomial model, described as: response to treatment at Week 24 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)	
Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.751
upper limit	1.078

Statistical analysis title	Estimate for relative risk
Statistical analysis description:	
Was to be analyzed using a log-linked binomial model, described as: response to treatment at Week 24 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)	
Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.725
upper limit	1.116

Secondary: Percentage of Patients With a Clinical Response (CDAI Decrease of ≥70 Compared With Baseline) at Week 24

End point title	Percentage of Patients With a Clinical Response (CDAI Decrease of ≥70 Compared With Baseline) at Week 24

End point description:

The CDAI is a validated instrument to measure disease severity in CD. The CDAI score is a sum of the 8 factors (number of liquid stools, abdominal pain, general well-being, extra-intestinal complications, antidiarrheal drugs, abdominal mass, hematocrit and body weight) after adjustment with a weighting factor. Higher CDAI scores indicating more active disease. The CDAI decrease at Week 24 was assessed as the decrease relative to baseline measurement, patients with a decrease ≥70 were responders. Percentage=least squares means per treatment group back transformed using inverse logit function. Missing data were imputed according to NRI and LOCF. The full analysis set (FAS) contained all randomized patients who received at least 1 dose of trial medication, and had all efficacy measures relevant for the CDAI, measured at baseline and at least once postbaseline.

End point type	Secondary

End point timeframe:

Week 24

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	72		
Units: Percentage				
number (not applicable)	87.4	87.4		

Statistical analyses

Statistical analysis title	Estimate for relative risk

Statistical analysis description:

Was to be analyzed using a log-linked binomial model, described as: response to treatment at Week 24 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)

Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.871
upper limit	1.148

Statistical analysis title	Estimate for relative risk

Statistical analysis description:

Was to be analyzed using a log-linked binomial model, described as: response to treatment at Week 24 = treatment+prior infliximab exposure+screening Simple Endoscopic Score for Crohn's Disease (SES-CD)

Comparison groups	BI 695501 v Humira EU
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.848
upper limit	1.178

Secondary: Percentage of Patients With Adverse Events (AEs), Serious AEs (SAEs), and AEs of Special Interest (AESIs)

End point title	Percentage of Patients With Adverse Events (AEs), Serious AEs (SAEs), and AEs of Special Interest (AESIs)

End point description:

Analysis of AEs focused on treatment-emergent AEs (TEAEs). For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. TEAEs and SAEs (including investigator-assessed trial medication-related TEAEs) and AESIs are reported. The following were considered an AESI: hepatic injury, anaphylactic reactions, serious infection and hypersensitivity reactions. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
TEAE -Period 1	62.5	56.0		
serious TEAE - Period 1	8.3	10.7		
AESI TEAE - Period 1	2.8	2.7		
TEAE - Period 2	43.1	45.3		
serious TEAE - Period 2	2.8	12.0		
AESI TEAE - Period 2	2.8	2.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Infections

End point title	Percentage of Patients With Infections

End point description:

The percentage of patients with TEAEs for infections and serious infections are reported. For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
Period 1	23.6	22.7		
Period 2	19.4	22.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Serious Infections

End point title	Percentage of Patients With Serious Infections

End point description:

The percentage of patients with TEAEs for infections and serious infections are reported. For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
Period 1	2.8	2.7		
Period 2	1.4	4.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Experienced Hypersensitivity Reactions

End point title	Percentage of Patients Who Experienced Hypersensitivity Reactions

End point description:

The percentage of patients with TEAEs for hypersensitivity reactions is reported. For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
Period 1	5.6	2.7		
Period 2	2.8	6.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Experienced Drug Induced Liver Injury (DILI)

End point title	Percentage of Patients Who Experienced Drug Induced Liver Injury (DILI)

End point description:

The percentage of patients with TEAEs for DILIs is reported. For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
Period 1	0.0	0.0		
Period 2	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Injection Site Reactions

End point title	Percentage of Patients With Injection Site Reactions

End point description:

The percentage of patients with TEAEs for injection site reactions is reported. For the period 1 'Baseline – Week 24', TEAEs were defined as AEs that started or worsened on or after first dose of trial medication and prior to date of the Week 24 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients who discontinued treatment before Week 24. For the period 2 'Week 24 – Week 46', TEAEs were defined as AEs that started or worsened on Week 24 visit and prior to or on Week 56 visit or within 10 weeks (70 days, inclusive) after last dose of trial medication for patients discontinuing treatment prior to Week 46. The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

End point type	Secondary

End point timeframe:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

End point values	BI 695501	Humira EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	75		
Units: Percentage				
number (not applicable)				
Period 1	0.0	6.7		
Period 2	1.4	1.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of trial medication until 10 weeks after last administration, up to a maximum of 56 weeks.

Adverse event reporting additional description:

The Safety Analysis Set (SAF) contained all randomized patients who received at least 1 dose (full or partial) of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	BI 695501 (Baseline - Week 24 + 10 Weeks [70 days])

Reporting group description:

Patients randomized to BI 695501 received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders (CDAI decrease of ≥70 compared to baseline), patients continued to receive BI 695501 every 2 weeks until the end of the treatment (EoT) period (Week 46). Patients were administered with a loading dose of 160 milligram (mg) BI 695501 on Day 1, followed by 80 mg BI 695501 2 weeks later (Day 15), and thereafter 40 mg BI 695501 every 2 weeks until Week 46. Trial medication was administered by subcutaneous (SC) injection.

Reporting group title	Humira (Baseline - Week 24 + 10 Weeks [70 days])

Reporting group description:

Patients randomized to EU-approved Humira received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders, patients continued to receive EU-approved Humira until Week 22 and then switched to receive BI 695501 every 2 weeks from Week 24 until the EoT period (Week 46). Patients were administered with a loading dose of 160 mg EU-approved Humira on Day 1, followed by 80 mg EU-approved Humira 2 weeks later (Day 15), and 40 mg EU-approved Humira every 2 weeks until Week 22. Patients were then switched to receive 40 mg BI 695501 every 2 weeks from Week 24 until Week 46. Trial medication was administered by SC injection.

Reporting group title	BI 695501 (Week 24 - Week 46 + 10 Weeks [70 days])

Reporting group description:

Patients randomized to BI 695501 received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders (CDAI decrease of ≥70 compared to baseline), patients continued to receive BI 695501 every 2 weeks until the end of the treatment (EoT) period (Week 46). Patients were administered with a loading dose of 160 milligram (mg) BI 695501 on Day 1, followed by 80 mg BI 695501 2 weeks later (Day 15), and thereafter 40 mg BI 695501 every 2 weeks until Week 46. Trial medication was administered by subcutaneous (SC) injection.

Reporting group title	Humira (Week 24 - Week 46 + 10 Weeks [70 days])

Reporting group description:

Patients randomized to EU-approved Humira received treatment every 2 weeks until Week 4 when they were assessed for clinical response. If classified as responders, patients continued to receive EU-approved Humira until Week 22 and then switched to receive BI 695501 every 2 weeks from Week 24 until the EoT period (Week 46). Patients were administered with a loading dose of 160 mg EU-approved Humira on Day 1, followed by 80 mg EU-approved Humira 2 weeks later (Day 15), and 40 mg EU-approved Humira every 2 weeks until Week 22. Patients were then switched to receive 40 mg BI 695501 every 2 weeks from Week 24 until Week 46. Trial medication was administered by SC injection.

Serious adverse events	BI 695501 (Baseline - Week 24 + 10 Weeks [70 days])	Humira (Baseline - Week 24 + 10 Weeks [70 days])	BI 695501 (Week 24 - Week 46 + 10 Weeks [70 days])
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 72 (8.33%)	8 / 75 (10.67%)	2 / 72 (2.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pregnancy, puerperium and perinatal conditions			
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	2 / 72 (2.78%)	5 / 75 (6.67%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Anal fistula			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0

Large intestinal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Palmoplantar pustulosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pruritus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pyoderma gangrenosum			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Rash erythematous			

subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Anal abscess			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Psoas abscess			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0

Rotavirus infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0

Serious adverse events	Humira (Week 24 - Week 46 + 10 Weeks [70 days])		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 75 (12.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal fistula			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis chronic			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palmoplantar pustulosis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pruritus				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyoderma gangrenosum				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash erythematous				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Joint swelling				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Acute sinusitis				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 75 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pulmonary tuberculosis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psoas abscess			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotavirus infection			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BI 695501 (Baseline - Week 24 + 10 Weeks [70 days])	Humira (Baseline - Week 24 + 10 Weeks [70 days])	BI 695501 (Week 24 - Week 46 + 10 Weeks [70 days])
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 72 (31.94%)	16 / 75 (21.33%)	13 / 72 (18.06%)
Investigations			
Weight increased			
subjects affected / exposed	4 / 72 (5.56%)	1 / 75 (1.33%)	3 / 72 (4.17%)
occurrences (all)	5	2	3
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	4 / 72 (5.56%)	3 / 75 (4.00%)	0 / 72 (0.00%)
occurrences (all)	4	3	0
Abdominal pain			
subjects affected / exposed	3 / 72 (4.17%)	2 / 75 (2.67%)	1 / 72 (1.39%)
occurrences (all)	4	2	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	6 / 72 (8.33%)	0 / 75 (0.00%)	2 / 72 (2.78%)
occurrences (all)	6	0	2
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	5 / 72 (6.94%)	3 / 75 (4.00%)	0 / 72 (0.00%)
occurrences (all)	5	3	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 72 (4.17%)	5 / 75 (6.67%)	2 / 72 (2.78%)
occurrences (all)	4	6	2
Nasopharyngitis			
subjects affected / exposed	2 / 72 (2.78%)	2 / 75 (2.67%)	5 / 72 (6.94%)
occurrences (all)	2	2	5

Non-serious adverse events	Humira (Week 24 - Week 46 + 10 Weeks [70 days])		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 75 (16.00%)		
Investigations			
Weight increased			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 75 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		
Upper respiratory tract infection			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2017	• Number of sites and countries were updated to reflect the current trial status. • It was clarified that the local hematocrit value was to be used to determine CDAI score at Week 4 (Visit 4) so that clinical response could be determined immediately, the hematocrit value from the central laboratory assessment at Week 8 (Visit 6) was to be used to determine CDAI at Week 12 (Visit 8), and weight was to be measured at all visits where physical examination was not being performed, for use in CDAI determination. • Inclusion criterion 1c was amended to make the severity of disease, as defined by CDAI, consistent with endoscopic evaluation. Eligible patients had to have evidence of mucosal ulcers in at least 1 segment of the ileum or colon. • The term "initial isolate ileitis" was updated to "isolated ileal disease". • Inclusion criterion 2 was amended to clarify that only infliximab was allowed as first-line anti-tumor necrosis factor (TNF) therapy; previous treatment with other anti-TNF therapies (specifically certolizumab) were not permitted. • The process to be used for primary analysis was clarified to state that efficacy data was to be included up to the Week 4 visit only and all available data for safety and other endpoints were to be included up to the data cut-off date. • Appendix 10.1 (Medication Blinding Procedure for Third Party Blinding) was updated to align the protocol with instructions included in the trial Pharmacy Manual.
12 December 2017	•Trial methodology and related statistical method, and sample size calculations were updated to reflect an exploratory trial design. The design change allowed trial objectives to be achieved with a smaller number of evaluable subjects (65 in each group) and reduced total sample size of approximately 130 (from approximately 286). • Tuberculosis(TB) testing: Additional TB testing was included for Week 24 (Visit 14), before switching from Humira to BI 6995501, to clarify whether incidence of possible positive TB tests was linked to the comparator or test product. New text was included to clarify TB testing and subsequent follow up during the trial and exclusion criterion 8 was updated to emphasize that TNF inhibitor use was allowed. • Exclusion criterion 10 was updated to remove reference to positive anti-adalimumab antibodies at baseline to clarify that results of antidrug antibodies were not available at time of inclusion. • Description of CDAI assessment was amended to clarify the days patients were required to keep a symptom diary prior to each assessment. • Text was added to End of Treatment visit description to state that in event of early discontinuation, a patient was to receive treatment as deemed appropriate by the investigator and in accordance with applicable guidance. • Appendix 10.1 (Medication Blinding Procedure for Third Party Blinding) was updated to clarify how to handle used syringes in accordance with medical requirements and to align the protocol with instructions included in the trial Pharmacy Manual. • Additional table footnote was added to Appendix 10.2 (List of Laboratory Tests) to clarify that pathogens other than mandatory list may have been identified. • Due to trial design change, additional text was included in Appendix 10.3 (Details About the Statistical Considerations) to clarify that standard rules for noninferiority margin selection were not to be applied but, magnitude of preserved historical treatment effect was to be used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported