Clinical trial results:
A phase II, multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel-group study to evaluate the efficacy, pharmacokinetics, and safety of BI 655066/ABBV-066 (risankizumab), an Interleukin [IL]-23 p19 antagonist monoclonal antibody, in patients with moderately to severely active Crohn's Disease, who are naïve to, or were previously treated with anti-Tumor Necrosis Factor [TNF] therapy

Summary

EudraCT number	2013-002902-29
Trial protocol	BE GB IE ES NL DE
Global end of trial date	18 November 2016

Results information

Result version number	v1 (current)
This version publication date	01 December 2017
First version publication date	01 December 2017

Trial information

Trial identification

Sponsor protocol code	1311.6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02031276
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, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, 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	13 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2015
Global end of trial reached?	Yes
Global end of trial date	18 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is a proof of concept, multi-center, randomized, double-blind, placebo-controlled, parallel-group phase 2 dose-ranging study of BI 655066, an IL-23 p19 antagonist monoclonal antibody, in patients with moderately to severely active Crohn's disease.

Protection of trial subjects:

Only subjects who 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	25 February 2014
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	Belgium: 38
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	121
EEA total number of subjects	91

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)	116
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized to 1 of 3 double-blind treatment arms in Period 1; those who achieved deep remission in Period 1 entered Period 2 washout; those who did not achieve deep remission in Period 1 entered Period 2 open-label (OL) treatment. Participants who were in clinical remission at the end of Period 2 continued to Period 3 OL treatment

Period 1

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

Blinding implementation details:

Period 1 was blinded intravenous (IV) therapy, period 2 was open label IV therapy and period 3 was open label subcutaneous (SC) therapy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Placebo IV (Period 1)

Arm description:

Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Placebo
Investigational medicinal product name	Placebo for risankizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo for risankizumab administered by IV infusion.

Arm title	Double-blind Risankizumab 200 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Risankizumab administered by IV infusion.

Arm title	Double-blind Risankizumab 600 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label

risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Risankizumab administered by IV infusion.

Number of subjects in period 1	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Started	39	41	41
Completed	33	35	40
Not completed	6	6	1
Adverse event, non-fatal	6	5	1
Not specified	-	1	-

Period 2

Period 2 title	Open-label Risankizumab IV
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

no re-randomisation was done

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Placebo (Period 1)

Arm description:

Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Risankizumab administered by IV infusion.

Arm title	Double-blind Risankizumab 200 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for

12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Risankizumab administered by IV infusion.

Arm title	Double-blind Risankizumab 600 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Risankizumab administered by IV infusion.

Number of subjects in period 2[1]	Double-blind Placebo (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Started	33	35	

Arm title	Double-blind Placebo IV (Period 1)

Arm description:

Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Risankizumab administered by SC infusion.

Arm title	Double-blind Risankizumab 200 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Risankizumab administered by SC infusion.

Arm title	Double-blind Risankizumab 600 mg IV (Period 1)

Arm description:

Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	
Other name	BI 655066, ABBV-066
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Risankizumab administered by SC infusion.

Number of subjects in period 3[2]	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Started	19	22	21
Completed	16	19	19
Not completed	3	3	2
Adverse event, non-fatal	-	2	-
Not specified	-	-	1
Withdrawal by subject	1	1	1

Protocol deviation	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: A total of 38 subjects did not enter Period 3 (not in clinical remission); 10 subjects in the Double-blind Placebo IV group, 11 subjects in the Double-blind Risankizumab 200 mg IV group, and 17 subjects in the Double-blind Risankizumab 600 mg IV group.

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Placebo IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Risankizumab 200 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.	
Reporting group title	Double-blind Risankizumab 600 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	

Reporting group values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Number of subjects	39	41	41
Age categorical Units: Subjects			
Age Continuous			
Full Analysis Set - Period 1 (FAS-P1): All randomized subjects who received at least 1 dose of study drug in the double-blind IV period (Period 1).			
Units: years			
arithmetic mean	35.5	38.8	39.9
standard deviation	± 13.86	± 13.27	± 13.26
Gender, Male/Female Units: Subjects			
Female	16	15	16
Male	23	26	25

Reporting group values	Total		
Number of subjects	121		
Age categorical Units: Subjects			
Age Continuous			
Full Analysis Set - Period 1 (FAS-P1): All randomized subjects who received at least 1 dose of study drug in the double-blind IV period (Period 1).			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	47		
Male	74		

End points

End points reporting groups

Reporting group title	Double-blind Placebo IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Risankizumab 200 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.	
Reporting group title	Double-blind Risankizumab 600 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Placebo (Period 1)
Reporting group description:	
Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Risankizumab 200 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.	
Reporting group title	Double-blind Risankizumab 600 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Placebo IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Reporting group title	Double-blind Risankizumab 200 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by in Period 3.	
Reporting group title	Double-blind Risankizumab 600 mg IV (Period 1)
Reporting group description:	
Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks in Period 1, followed by open-label risankizumab 600 mg IV in Period 2, then open-label risankizumab 180 mg by subcutaneous (SC) injection in Period 3.	
Subject analysis set title	Double-blind Placebo IV (Period 1)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants randomized to receive double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks.	
Subject analysis set title	Double-blind Risankizumab 200 mg IV (Period 1)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to receive double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks.

Subject analysis set title	Double-blind Risankizumab 600 mg IV (Period 1)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to receive double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks.

Subject analysis set title	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants randomized to receive double-blind risankizumab 200 mg and 600 mg by intravenous (IV) injection for 12 weeks.

Primary: Percentage of participants achieving CDAI Clinical Remission at week 12

End point title	Percentage of participants achieving CDAI Clinical Remission at week 12

End point description:

The CDAI is a measure of clinical response and remission. The CDAI includes 8 variables encompassing both patient-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight) variables. For symptoms scores, patients keep track of daily symptoms on a diary card and the daily symptom scores are summed for the week. Each item in the CDAI is assigned a specific weight, and the weighted values of the items are totaled to produce the CDAI. Higher CDAI scores indicate greater disease activity, with a lower limit of 0 and no set upper limit: < 150 indicates remission, 150 - 219 indicates mildly active disease, 220 - 450 indicates moderately active disease, and > 450 indicates severely active disease. CDAI clinical remission is defined as CDAI < 150 at Week 12. Nonresponder Imputation (NRI): Missing values were counted as nonresponders.

End point type	Primary

End point timeframe:

Week 12

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[1]	41[2]	41[3]	82[4]
Units: Percentage of participants				
number (confidence interval 95%)	15.4 (5.9 to 30.5)	19.5 (8.8 to 34.9)	36.6 (22.1 to 53.1)	28.0 (18.7 to 39.1)

Notes:

[1] - FAS-P1

[2] - FAS-P1

[3] - FAS-P1

[4] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified by anti-tumor necrosis factor (anti-TNF) exposure.

Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0955
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	27.5

Secondary: Percentage of Participants Achieving CDAI Clinical Response at Week 12

End point title	Percentage of Participants Achieving CDAI Clinical Response at Week 12

End point description:

The CDAI is a measure of clinical response and remission. The CDAI includes 8 variables encompassing both patient-reported (symptoms, general well-being) and objective (medication usage, laboratory variables, presence of abdominal mass or complications, and weight) variables. For symptoms scores, patients keep track of daily symptoms on a diary card and the daily symptom scores are summed for the week. Each item in the CDAI is assigned a specific weight, and the weighted values of the items are totaled to produce the CDAI. Higher CDAI scores indicate greater disease activity, with a lower limit of 0 and no set upper limit: < 150 indicates remission, 150 - 219 indicates mildly active disease, 220 - 450 indicates moderately active disease, and > 450 indicates severely active disease. CDAI clinical response is defined as either a CDAI < 150 or a CDAI reduction from Baseline of at least 100 points at Week 12. NRI: Missing values were counted as nonresponders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[5]	41[6]	41[7]	82[8]
Units: Percentage of participants				
number (confidence interval 95%)	23.1 (11.1 to 39.3)	31.7 (18.1 to 48.1)	41.5 (26.3 to 57.9)	36.6 (26.2 to 48.0)

Notes:

[5] - FAS-P1

[6] - FAS-P1

[7] - FAS-P1

[8] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified

by anti-TNF exposure.

Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1151
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	13.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	30.1

Secondary: Percentage of Participants Achieving Crohn's Disease Endoscopic Activity Index of Severity (CDEIS) Remission at Week 12

End point title	Percentage of Participants Achieving Crohn's Disease Endoscopic Activity Index of Severity (CDEIS) Remission at Week 12

End point description:

CDEIS is an index for determining the severity of Crohn's disease with endoscopic localization to ileum and colon. CDEIS considers 4 parameters (deep ulcerations, superficial ulcerations, surface involved by disease, and surface involved by ulcerations), each one evaluated in 5 pre-defined segments of the colon (ileum, ascending colon, transverse colon, descending colon and sigmoid loop, and rectum). The results of the individual segments of the colon are divided by the number of segments investigated; the presence of stenosis increases the score at the end of the computation. CDEIS remission is defined as a CDEIS ≤ 4 (or, for patients with initial isolated ileitis, a CDEIS ≤ 2) at Week 12. NRI: Missing values were counted as nonresponders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[9]	41[10]	41[11]	82[12]
Units: Percentage of participants				
number (confidence interval 95%)	2.6 (0.1 to 13.5)	9.8 (2.7 to 23.1)	19.5 (8.8 to 34.9)	14.6 (7.8 to 24.2)

Notes:

[9] - FAS-P1

[10] - FAS-P1

[11] - FAS-P1

[12] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified by anti-TNF exposure.	
Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0057
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	20.6

Secondary: Percentage of Participants Achieving CDEIS Response at Week 12

End point title	Percentage of Participants Achieving CDEIS Response at Week 12
End point description:	
CDEIS is an index for determining the severity of Crohn's disease with endoscopic localization to ileum and colon. CDEIS considers 4 parameters (deep ulcerations, superficial ulcerations, surface involved by disease, and surface involved by ulcerations), each one evaluated in 5 pre-defined segments of the colon (ileum, ascending colon, transverse colon, descending colon and sigmoid loop, and rectum). The results of the individual segments of the colon are divided by the number of segments investigated; the presence of stenosis increases the score at the end of the computation. CDEIS response is defined as defined as ≥ 50% reduction of CDEIS from Baseline to Week 12. NRI: Missing values were counted as nonresponders.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[13]	41[14]	41[15]	82[16]
Units: Percentage of participants				
number (confidence interval 95%)	12.8 (4.3 to 27.4)	26.8 (14.2 to 42.9)	36.6 (22.1 to 53.1)	31.7 (21.9 to 42.9)

Notes:

[13] - FAS-P1

[14] - FAS-P1

[15] - FAS-P1

[16] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified by anti-TNF exposure.	
Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0104
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.4
upper limit	33

Secondary: Percentage of Participants Achieving Mucosal Healing at Week 12

End point title	Percentage of Participants Achieving Mucosal Healing at Week 12
End point description:	
Mucosal healing was defined as the absence of mucosal ulceration, i.e., a CDEIS ulceration sub-score (deep ulceration, superficial ulceration, ulcerated stenosis) of 0 at Week 12. NRI: Missing values were counted as nonresponders.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[17]	41[18]	41[19]	82[20]
Units: Percentage of participants				
number (confidence interval 95%)	2.6 (0.1 to 13.5)	2.4 (0.1 to 12.9)	7.3 (1.5 to 19.9)	4.9 (1.3 to 12.0)

Notes:

[17] - FAS-P1

[18] - FAS-P1

[19] - FAS-P1

[20] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified by anti-TNF exposure.	
Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4977
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	9.2

Secondary: Percentage of Participants Achieving Deep Remission at Week 12	
End point title	Percentage of Participants Achieving Deep Remission at Week 12
End point description:	
Deep remission is defined as clinical remission (CDAI < 150) AND CDEIS remission (CDEIS ≤ 4, or ≤ 2 in participants with initial isolated ileitis) at Week 12. NRI: missing values were counted as nonresponders.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)	Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[21]	41[22]	41[23]	82[24]
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 9.0)	2.4 (0.1 to 12.9)	12.2 (4.1 to 26.2)	7.3 (2.7 to 15.2)

Notes:

[21] - FAS-P1

[22] - FAS-P1

[23] - FAS-P1

[24] - FAS-P1

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Statistics for the difference are calculated using the Cochran-Mantel-Haenszel risk difference stratified by tumor necrosis factor (TNF)-exposure.

Comparison groups	Double-blind Placebo IV (Period 1) v Double-blind Risankizumab 200 + 600 mg IV (Period 1)
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0107
Method	Cochran-Mantel-Haenszel
Parameter estimate	difference in percentage of participants
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	13

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) and serious adverse events (TESAEs) were collected from the first dose of study drug until 15 weeks after the last dose of study drug (up to 67 weeks).

Adverse event reporting additional description:

TEAEs and TESAEs: AEs and SAEs with onset/worsening from the first dose of DB study drug until either the first dose of OL risankizumab or 15 weeks after the last dose of DB study drug (up to 27 weeks); for All Risankizumab, from the first dose of DB or OL risankizumab until 15 weeks after the last dose of risankizumab (up to 67 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Double-blind Placebo IV (Period 1)

Reporting group description:

Participants received double-blind placebo for risankizumab by intravenous (IV) injection for 12 weeks.

Reporting group title	Double-blind Risankizumab 200 mg IV (Period 1)

Reporting group description:

Participants received double-blind risankizumab 200 mg by intravenous (IV) injection for 12 weeks.

Reporting group title	Double-blind Risankizumab 600 mg IV (Period 1)

Reporting group description:

Participants administered double-blind risankizumab 600 mg by intravenous (IV) injection for 12 weeks.

Reporting group title	Open-label Risankizumab 600 mg IV (Period 2)

Reporting group description:

Participants administered open-label risankizumab 600 mg by intravenous (IV) injection for 12 weeks.

Reporting group title	Open-label Risankizumab 180 mg SC (Period 3)

Reporting group description:

Participants administered open-label risankizumab 600 mg by subcutaneous (SC) injection for 12 weeks.

Reporting group title	All Risankizumab

Reporting group description:

Participants administered at least one dose of risankizumab.

Serious adverse events	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
PAIN			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
PYREXIA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX			

subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Psychiatric disorders			
PSYCHIATRIC DECOMPENSATION			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD MAGNESIUM DECREASED			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Nervous system disorders			
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			

subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MIGRAINE			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Ear and labyrinth disorders			
SUDDEN HEARING LOSS			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
BLINDNESS TRANSIENT			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIPLOPIA			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ANAL FISTULA			

subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
APHTHOUS ULCER			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
CROHN'S DISEASE			
subjects affected / exposed	5 / 39 (12.82%)	2 / 41 (4.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	2 / 6	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCTALGIA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Renal and urinary disorders			

ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
RENAL COLIC			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
RENAL FAILURE			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
ANAL ABSCESS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISION SITE ABSCESS			

subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ABSCESS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
VAGINAL ABSCESS			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (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
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALNUTRITION			

subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	0 / 41 (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

Serious adverse events	Open-label Risankizumab 600 mg IV (Period 2)	Open-label Risankizumab 180 mg SC (Period 3)	All Risankizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 101 (10.89%)	7 / 62 (11.29%)	31 / 115 (26.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			

subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PNEUMOTHORAX			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
PSYCHIATRIC DECOMPENSATION			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD MAGNESIUM DECREASED			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
TACHYCARDIA			

subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MIGRAINE			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
SUDDEN HEARING LOSS			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Eye disorders			
BLINDNESS TRANSIENT			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIPLOPIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ANAL FISTULA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APHTHOUS ULCER			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CROHN'S DISEASE			
subjects affected / exposed	3 / 101 (2.97%)	1 / 62 (1.61%)	7 / 115 (6.09%)
occurrences causally related to treatment / all	1 / 4	0 / 1	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 101 (1.98%)	1 / 62 (1.61%)	3 / 115 (2.61%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	2 / 115 (1.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCTALGIA			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	0 / 101 (0.00%)	1 / 62 (1.61%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISION SITE ABSCESS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ABSCESS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VAGINAL ABSCESS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
		0 / 0	0 / 0

subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALNUTRITION			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	2 / 115 (1.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
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	Double-blind Placebo IV (Period 1)	Double-blind Risankizumab 200 mg IV (Period 1)	Double-blind Risankizumab 600 mg IV (Period 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 39 (71.79%)	25 / 41 (60.98%)	21 / 41 (51.22%)
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	2 / 39 (5.13%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	3 / 41 (7.32%)
occurrences (all)	1	1	4
HEADACHE			
subjects affected / exposed	5 / 39 (12.82%)	6 / 41 (14.63%)	5 / 41 (12.20%)
occurrences (all)	6	7	7
LETHARGY			

subjects affected / exposed	3 / 39 (7.69%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	4
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 39 (5.13%)	4 / 41 (9.76%)	2 / 41 (4.88%)
occurrences (all)	3	5	2
FATIGUE			
subjects affected / exposed	3 / 39 (7.69%)	0 / 41 (0.00%)	2 / 41 (4.88%)
occurrences (all)	3	0	2
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	2 / 39 (5.13%)	1 / 41 (2.44%)	2 / 41 (4.88%)
occurrences (all)	2	1	2
MALAISE			
subjects affected / exposed	0 / 39 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
PERIPHERAL SWELLING			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences (all)	4	0	0
PYREXIA			
subjects affected / exposed	3 / 39 (7.69%)	3 / 41 (7.32%)	3 / 41 (7.32%)
occurrences (all)	3	4	3
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	5 / 39 (12.82%)	6 / 41 (14.63%)	4 / 41 (9.76%)
occurrences (all)	5	6	4
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
CROHN'S DISEASE			
subjects affected / exposed	1 / 39 (2.56%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
DIARRHOEA			

subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	3 / 41 (7.32%)
occurrences (all)	3	2	3
HAEMATOCHEZIA			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	2
NAUSEA			
subjects affected / exposed	4 / 39 (10.26%)	9 / 41 (21.95%)	4 / 41 (9.76%)
occurrences (all)	4	9	4
VOMITING			
subjects affected / exposed	4 / 39 (10.26%)	4 / 41 (9.76%)	2 / 41 (4.88%)
occurrences (all)	4	4	2
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 39 (10.26%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences (all)	5	1	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 39 (2.56%)	2 / 41 (4.88%)	1 / 41 (2.44%)
occurrences (all)	1	2	1
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	3 / 41 (7.32%)
occurrences (all)	0	1	3
SLEEP DISORDER			
subjects affected / exposed	2 / 39 (5.13%)	1 / 41 (2.44%)	0 / 41 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	4 / 39 (10.26%)	6 / 41 (14.63%)	8 / 41 (19.51%)
occurrences (all)	4	6	10
BACK PAIN			
subjects affected / exposed	2 / 39 (5.13%)	1 / 41 (2.44%)	3 / 41 (7.32%)
occurrences (all)	2	1	5

PAIN IN EXTREMITY			
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	1 / 41 (2.44%)
occurrences (all)	2	2	1
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	3 / 39 (7.69%)	2 / 41 (4.88%)	2 / 41 (4.88%)
occurrences (all)	4	3	2
SINUSITIS			
subjects affected / exposed	0 / 39 (0.00%)	1 / 41 (2.44%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 39 (5.13%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
HYPOKALAEMIA			
subjects affected / exposed	3 / 39 (7.69%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences (all)	3	0	1

Non-serious adverse events	Open-label Risankizumab 600 mg IV (Period 2)	Open-label Risankizumab 180 mg SC (Period 3)	All Risankizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 101 (47.52%)	31 / 62 (50.00%)	80 / 115 (69.57%)
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	3 / 101 (2.97%)	0 / 62 (0.00%)	4 / 115 (3.48%)
occurrences (all)	3	0	4
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	5 / 101 (4.95%)	1 / 62 (1.61%)	9 / 115 (7.83%)
occurrences (all)	5	1	11
HEADACHE			
subjects affected / exposed	7 / 101 (6.93%)	6 / 62 (9.68%)	22 / 115 (19.13%)
occurrences (all)	10	7	31
LETHARGY			
subjects affected / exposed	2 / 101 (1.98%)	1 / 62 (1.61%)	2 / 115 (1.74%)
occurrences (all)	2	1	3
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	2 / 101 (1.98%)	1 / 62 (1.61%)	6 / 115 (5.22%)
occurrences (all)	2	1	7
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	3 / 101 (2.97%)	1 / 62 (1.61%)	9 / 115 (7.83%)
occurrences (all)	3	1	11
FATIGUE			
subjects affected / exposed	2 / 101 (1.98%)	5 / 62 (8.06%)	8 / 115 (6.96%)
occurrences (all)	2	5	9
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	3 / 115 (2.61%)
occurrences (all)	0	0	3
MALAISE			
subjects affected / exposed	4 / 101 (3.96%)	2 / 62 (3.23%)	7 / 115 (6.09%)
occurrences (all)	4	2	7
PERIPHERAL SWELLING			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	0 / 115 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	6 / 101 (5.94%)	3 / 62 (4.84%)	14 / 115 (12.17%)
occurrences (all)	7	3	17
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	11 / 101 (10.89%)	5 / 62 (8.06%)	21 / 115 (18.26%)
occurrences (all)	12	6	28
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 101 (1.98%)	3 / 62 (4.84%)	8 / 115 (6.96%)
occurrences (all)	2	3	8
CROHN'S DISEASE			
subjects affected / exposed	0 / 101 (0.00%)	4 / 62 (6.45%)	4 / 115 (3.48%)
occurrences (all)	0	4	4
DIARRHOEA			
subjects affected / exposed	4 / 101 (3.96%)	1 / 62 (1.61%)	9 / 115 (7.83%)
occurrences (all)	5	1	11
HAEMATOCHEZIA			

subjects affected / exposed	2 / 101 (1.98%)	1 / 62 (1.61%)	4 / 115 (3.48%)
occurrences (all)	2	2	6
NAUSEA			
subjects affected / exposed	6 / 101 (5.94%)	1 / 62 (1.61%)	18 / 115 (15.65%)
occurrences (all)	6	1	20
VOMITING			
subjects affected / exposed	7 / 101 (6.93%)	0 / 62 (0.00%)	11 / 115 (9.57%)
occurrences (all)	8	0	14
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	3 / 101 (2.97%)	3 / 62 (4.84%)	7 / 115 (6.09%)
occurrences (all)	3	3	7
OROPHARYNGEAL PAIN			
subjects affected / exposed	4 / 101 (3.96%)	2 / 62 (3.23%)	8 / 115 (6.96%)
occurrences (all)	4	2	9
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	3 / 101 (2.97%)	0 / 62 (0.00%)	4 / 115 (3.48%)
occurrences (all)	3	0	4
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	1 / 101 (0.99%)	2 / 62 (3.23%)	6 / 115 (5.22%)
occurrences (all)	1	2	7
SLEEP DISORDER			
subjects affected / exposed	0 / 101 (0.00%)	0 / 62 (0.00%)	1 / 115 (0.87%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	7 / 101 (6.93%)	6 / 62 (9.68%)	25 / 115 (21.74%)
occurrences (all)	7	6	29
BACK PAIN			
subjects affected / exposed	3 / 101 (2.97%)	2 / 62 (3.23%)	9 / 115 (7.83%)
occurrences (all)	3	2	11
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 101 (0.99%)	0 / 62 (0.00%)	4 / 115 (3.48%)
occurrences (all)	1	0	4

Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	8 / 101 (7.92%)	9 / 62 (14.52%)	18 / 115 (15.65%)
occurrences (all)	9	13	27
SINUSITIS			
subjects affected / exposed	2 / 101 (1.98%)	3 / 62 (4.84%)	7 / 115 (6.09%)
occurrences (all)	2	3	7
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 101 (0.99%)	1 / 62 (1.61%)	3 / 115 (2.61%)
occurrences (all)	1	1	3
HYPOKALAEMIA			
subjects affected / exposed	2 / 101 (1.98%)	0 / 62 (0.00%)	2 / 115 (1.74%)
occurrences (all)	2	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2014	The protocol amendment included. [a] Replaced “Week 26” by “visit E1” when appropriate, removed “Drug screening”, added evaluation of Adverse Event (AE) at visit 1.1 [Flow Chart A (Blinded Intravenous Therapy (Period 1))], added “during period 1” to footnote 1 of Flow Chart A, added assessment of eligibility at visit 2, added fecal samples in the list of other sampling and testing. [b] Replaced “months” by “weeks”. [c] Exclusion criterion number 21 added per Health Authority request. [d] Reference to section 5.1.2 (Assessment of Efficacy) was added to clarify which hematocrit result should be used for calculation of Crohn’s Disease Activity Index (CDAI). [e] Clarification was added to footnote 6 of Flow Chart A. [f] The amendment included “Assessment of AE after subcutaneous injections will also include assessment of local tolerability. The assessment of local tolerability should be done just before the patient leaves the investigator site.” [g] If, in the investigator’s opinion, the patient required additional medical therapy for their Crohn’s Disease due to persistently high disease activity or worsening based on CDAI score (>450, or an increase by 100 points from baseline), the study treatment may be stopped and patients may receive conventional treatment for active disease as per investigator’s judgment. [h] Section 4.1.3 (Selection of doses in the trial) was amended. [i] Replaced “normal saline (0.9% NaCl)” by “5% Dextrose in Water (D5W)”. [j] The detailed procedures for preparing and handling the study drug were provided in Investigator Site File (ISF). [k] Section 5.6 [Biomarker (s)] was amended. [l] Additional unscheduled visits for the purpose of re-testing of laboratory parameters or AE monitoring were included as deemed necessary by the investigator. [m] To remove CDAI, Inflammatory Bowel Disease Questionnaire (IBDQ) and Crohn’s Disease Endoscopic Index of Severity (CDEIS) from the protocol.
27 May 2014	The protocol amendment included. a) Contact detail for Nasri Abdallah was updated and Ivona Herichova was added as Trial Clinical Monitor (TCM). b) Reference to ISF added. Intravenous (IV) infusions, as detailed in the Instructions for Preparation and Handling of BI 655066/Placebo in the Investigator Site File. c) Instruction how to proceed in case of Infusion reaction added. In case of infusion reactions emerging during or after infusion of BI 655066 or Placebo, the investigator should consider in accordance with severity of the reaction and local standard of care to 1) Immediately interrupt the infusion 2) Treat with systemic anti-histamines and intravenous steroids. Based on patient`s clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate reactions (according to RCTC grading in appendix 10.3) at lower speed with gradual increase to complete the infusion as detailed out in the Instructions for Preparation and Handling of BI 655066/Placebo in the Investigator Site File. d) Added recommendations in case of infusion reaction. In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading and proceed as described in Section 4.2.1 (Rescue medication, emergency procedures, and additional treatment(s)).

30 July 2014	The protocol amendment included. a) Change in TCM, TCM Nasri Abdallah was replaced by Ivona Herichova. b) Endoscopic remission criterion added for patients with initial isolated ileitis. c) Inclusion Criterion for Period 3 more specified. d) To add inclusion criteria for roll-over trial. e) To add CDEIS threshold for patients with initial isolated ileitis. f) Update on start point of oral corticosteroids tapering. g) To specify inclusion criteria (CDEIS score) for patients with isolated ileitis. h) The inclusion criteria for treatment experienced patients was simplified to clarify that stopping of previous anti-TNF treatment for other reason is not exclusionary. i) Editorial change - to add restriction on concomitant medication into the exclusion criteria. j) Editorial change – Deletion of the exclusion criteria #20 since is already added to exclusion criteria #4. k) To specify inclusion criteria (CDEIS score) for patients with isolated ileitis as is stated in rationale for change 7. l) This exclusion criterion #21 is added due to a harmonization across the project. m) To update secondary efficacy endpoints. To update other efficacy endpoint, rationale as for change 14. n) To fecal calprotectin and lactoferrin are collected for the analysis of biomarkers. o) The times of visit clarification. p) To add eligibility criteria and timing for roll-over from trial 1311.6 to 1311.20. q) To exclude assessments obligation. r) Justification of CDEIS scoring for patients with isolated ileitis. s) Reasoning for adding SES-CD and PRO-2. t) To add opioids to restricted medication. u) To add Guidelines on tapering of corticosteroids. v) To add PRO-2 description, which is likely to be the new FDA requested primary endpoint in CD trials. w) To clarify procedure in case of CDEIS/SES-CD discrepancies.
04 December 2014	The protocol amendment included. a) Information about roll over trial inserted in Clinical Trial Protocol (CTP) version 3 was deleted considering postponing of roll over study start. b) Emphasize that CDEI assessment is mandatory at visits R0 or E1only at certain circumstances. c) Administrative change: Reformulation of footnotes 6 and 7 wording to make them more clear for the readers. d) Sponsor decision on CDEIS score rounding. e) To cover intra-articular administration. f) Sponsor decision to not apply unblinding rules. g) Administrative change: Inconsistency correction, to be compliant with section 3.1 [Overall trial design and plan]. h) Administrative change: correction of incorrect statement. i) Sponsor decision to allow re-screening for specified patients. j) Administrative change: More appropriate name assignment to differentiate between Clinical and PRO response.
14 April 2015	The protocol amendment included. a) Vedolizumab deleted from the list of drugs requiring 6 months of wash-out in exclusion criterion #4. b) Rewording as per request from Korean HA to make the statement more clear: Rectal 5-ASA compounds, parenteral or rectal corticosteroids must have been discontinued at least 4 weeks prior to visit 2. Rectal 5-ASA compounds, parenteral or rectal corticosteroids within 4 weeks prior to visit 2. c) Change in calculation, weekly weighted average instead of daily weighted average. d) Additional other efficacy endpoints added. e) Added: “The trial bioanalyst (TBA) and bioanalytical laboratory will be unblinded and provided with randomization codes in order to support PK/ADA sample bioanalysis.” f) Cannabis added to restricted medication list due to rather common use in the population and the interference with key efficacy endpoints. g) Clarification of alternative treatment added: “1). Re-screening of patients will not be allowed unless they have received and failed alternative treatment after first SF now meet eligibility criteria. “ changed to: “Re-screening of patients will not be allowed unless they have received and failed alternative treatment (not limited to Anti-TNF) and started to meet eligibility criteria.”

30 July 2015	The protocol amendment included. a) Administrative change: Sponsor includes the changes implemented in the Investigator's Brochure (IB), version 6, dated 03 June 2015. b) Administrative change, sponsor decision on efficacy endpoints categorization c) Administrative change: correction of mistake in definition of CDEIS response and the typo correction in the week of endoscopic assessment should be week 52. d) Administrative change: typo correction - mistake in the week of endoscopic assessment, should be week 52. e) Deleted endpoints: Change in SES-CD at week 26. Change in CDEIS at week 26. f) Added information about blinding procedure for the Interim analysis: An interim analysis for planning purposes only will be performed when approximately 90 out of 120 patients will complete week 12 assessment. The Trial Statistical Analysis Plan (TSAP) will be approved before the interim analysis snapshot BI personnel specified in the Interim Analysis Logistic plan will have access to selected unblinded information necessary to perform and interpret the Interim analysis Internal Planning. The results of this interim analysis will be used for planning purposes only. g) Analysis for Internal Planning. An interim analysis for efficacy will be performed for the first approximately 90 patients out of the 120 targeted patients who complete the week 12 visit. This analysis is for internal planning purposes only to facilitate further substance development. No need to account for an alpha penalty since this analysis is for internal planning only, it will not affect the conduct of the current trial and the conclusion of the trial will be based on the primary analysis. Details of this interim analysis are specified in the interim analysis logistic plan which will be finalized before the fast track approval snapshot will be performed. The results will be documented separately, no interim analysis CTR will be written.
13 November 2015	The protocol amendment included. a) Patients fulfilling eligibility criteria for long term extension roll-over trial (1311.20) can be entered directly to 1311.20 trial after completion either visit E1 or E5 in 1311.6. b) Boolean remission endpoint added because it is a new way grouping CDAI subscores which was defined in the statistical plan. The analysis by visit was added for CDAI and PRO-2 which means a more detailed look at the data. c) The primary efficacy endpoint is the clinical remission of Crohn's Disease defined as a CDAI score of below 150 after 12 weeks. Changed to: The primary efficacy endpoint is the clinical remission of Crohn's Disease after 12 weeks, defined as a CDAI score of below 150. d) Added wording: The Simple Endoscopic Score in Crohn`s Disease (SES-CD) (R14-2969), has also been validated for CD and correlates closely with CDEIS, despite its reduced complexity. e) Follow up period is 15 weeks after the last administration of study medication. Changed to: Follow up period is 15 weeks after the last administration of study medication. Patients rolling over to 1311.20 trial are not requested to complete follow up period and are not counted as premature discontinuations. f) The statistical model for the binary endpoint is a stratified Cochran-Mantel-Haenszel test with randomisation factor of naïve or experienced to TNF antagonists as the stratification variable. There are three treatment arms, A is BI 655066 600 mg IV, B is BI 655066 200 mg IV, while C is the placebo arm. Changed to: The statistical model for the binary endpoint is a stratified Cochran-Mantel-Haenszel test with naïve or experienced to TNF antagonists as the stratification variable. There are three treatment arms, A is BI 655066 600 mg IV, B is BI 655066 200 mg IV, while C is the placebo arm. g) Adding comparison against placebo for clarification. Also, due to anticipated low number of patients in the TNF naïve group, an additional analysis is mentioned.

14 October 2016	The protocol amendment included. a) Changed “Boehringer Ingelheim” into “AbbVie/Boehringer Ingelheim”. b) Added ABBV-066 (risankizumab) after BI 655066. c) “The trial is sponsored by Boehringer Ingelheim (BI)” was changed to “The trial is sponsored by AbbVie in the US and Boehringer Ingelheim (BI) ex-US. (d) “Data Management and Statistical Evaluation will be done by BI according to BI SOPs” was changed to “Data Management will be done by BI according to BI SOPs and the Statistical Evaluation will be done by AbbVie according to their SOPs.” e) The sample for DNA banking will be stored at Boehringer Ingelheim for 15 years after the end of the clinical trial or until there is no more material available for tests” was changed to “The sample for DNA banking will be stored at AbbVie or a third party delegate (e.g. Boehringer Ingelheim Pharma GmbH & Co. KG; Birkendorfer Str. 65, 88397 Biberach, Germany).” for 15 years after the end of the clinical trial or until there is no more material available for tests.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported