Clinical trial results:
A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI 655130 (SPESOLIMAB) Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy

Summary

EudraCT number	2017-004230-28
Trial protocol	AT BE DE GB ES NL DK GR HU CZ IT
Global end of trial date	18 May 2020

Results information

Result version number	v1 (current)
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	1368-0005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03482635
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 Centre, Boehringer Ingelheim, 01 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Centre, Boehringer Ingelheim, 01 18002430127, 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	17 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2020
Global end of trial reached?	Yes
Global end of trial date	18 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives of Part 1 (Phase II) were to prove the concept of clinical activity of BI 655130 (spesolimab) as an induction therapy in patients with moderate-to-severely active ulcerative colitis who had failed previous biologic treatments and to identify efficacious and safe dose regimens.
The objectives of Part 2 (Phase III) would have been to confirm efficacy and safety of BI 655130 (spesolimab) in the same patient population and to provide the target population for the randomised withdrawal study 1368-0020. Due to recruitment issues, the sponsor decided to terminate this trial prematurely before Part 2 was started.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2018
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	Austria: 4
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	127
EEA total number of subjects	50

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)	119
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Phase II/III randomized, placebo-controlled, double-blind trial to assess the safety and efficacy of spesolimab induction therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy. Phase III was not conducted because the trial was prematurely discontinued due to recruitment issues.

Pre-assignment

Screening details:

Only subjects that met all the study inclusion and non 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 troughout the trial conduct. Rescue medication was allowed for all patients as required.

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

Blinding implementation details:

The randomisation codes were provided to bioanalytics prior to last patient out on Part 1 to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bioanalytics did not disclose the randomisation code or the results of individual measurements until official unblinding to the sponsor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

A solution of placebo was administered as intravenous infusion once every 4 weeks over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

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

Dosage and administration details:

A solution of placebo was administered as intravenous infusion once every 4 weeks over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Arm title	300 mg Spesolimab (BI 655130) SD

Arm description:

A single dose (SD) of 300 milligram (mg) solution of spesolimab was administered as intravenous infusion at week 0 in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

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

Dosage and administration details:

A single dose (SD) of 300 milligram (mg) solution of spesolimab was administered as intravenous infusion at week 0 in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Arm title	450 mg Spesolimab (BI 655130) q4w

Arm description:

450 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

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

Dosage and administration details:

450 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Arm title	1200 mg Spesolimab (BI 655130) q4w

Arm description:

1200 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

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

Dosage and administration details:

1200 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Number of subjects in period 1[1]	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w
Started	23	24	23
Treated	23	24	23
Completed	18	21	22
Not completed	5	3	1
Consent withdrawn by subject	2	1	-
Adverse event, non-fatal	2	2	-
Withdrawn by Principle Investigator	1	-	-
Lack of efficacy	-	-	1
Not treated	-	-	-

Number of subjects in period 1[1]	1200 mg Spesolimab (BI 655130) q4w
Started	28
Treated	27
Completed	20
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	3
Withdrawn by Principle Investigator	-
Lack of efficacy	3
Not treated	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Overall 127 subjects were enrolled in the trial, wereof 98 subjects actually started the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
A solution of placebo was administered as intravenous infusion once every 4 weeks over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	300 mg Spesolimab (BI 655130) SD
Reporting group description:	
A single dose (SD) of 300 milligram (mg) solution of spesolimab was administered as intravenous infusion at week 0 in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	450 mg Spesolimab (BI 655130) q4w
Reporting group description:	
450 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	1200 mg Spesolimab (BI 655130) q4w
Reporting group description:	
1200 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	

Reporting group values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w
Number of subjects	23	24	23
Age categorical			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
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)	22	23	22
From 65-84 years	1	1	1
85 years and over	0	0	0
Age Continuous			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: years			
arithmetic mean	42.2	41.4	42.3
standard deviation	± 14.1	± 14.6	± 15.3
Sex: Female, Male			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
Female	11	7	10
Male	12	17	13

Race (NIH/OMB)			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	1	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	18	23	18
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	23	24	23
Unknown or Not Reported	0	0	0

Reporting group values	1200 mg Spesolimab (BI 655130) q4w	Total	
Number of subjects	28	98	
Age categorical			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	25	92	
From 65-84 years	3	6	
85 years and over	0	0	
Age Continuous			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: years			
arithmetic mean	43.9		
standard deviation	± 14.9	-	
Sex: Female, Male			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
Female	8	36	
Male	20	62	
Race (NIH/OMB)			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			

American Indian or Alaska Native	1	1	
Asian	5	14	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	3	
White	21	80	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Randomised Set (RS): The RS included all randomised patients. Treatment assignment was as randomised. It was the main analysis set for presentation of efficacy on binary endpoints.			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	27	97	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
A solution of placebo was administered as intravenous infusion once every 4 weeks over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	300 mg Spesolimab (BI 655130) SD
Reporting group description:	
A single dose (SD) of 300 milligram (mg) solution of spesolimab was administered as intravenous infusion at week 0 in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	450 mg Spesolimab (BI 655130) q4w
Reporting group description:	
450 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	
Reporting group title	1200 mg Spesolimab (BI 655130) q4w
Reporting group description:	
1200 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.	

Primary: Proportion of patients with Clinical Remission at week 12

End point title	Proportion of patients with Clinical Remission at week 12
End point description:	
Proportion of patients with Clinical Remission (defined as modified Mayo Clinical Score (MCS) ≤ 2, with Stool frequency score (SFS) = 0 or 1 [if drop ≥1 from baseline] and Rectal Bleeding Score (RBS) = 0 and modified Endoscopic Subscore (mESS) ≤ 1) at week 12. Proportion of patients was calculated as n/N, with n=number of patients with Clinical Remission at week 12 and N=number analyzed. 95% Confidence Intervals (CI) were calculated using the method of Wilson. Randomised Set - Non Response Imputation (RS-NRI): The randomised set included all randomised patients, including patients with non-response imputation.	
End point type	Primary
End point timeframe:	
At week 12.	

End point values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w	1200 mg Spesolimab (BI 655130) q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[1]	24[2]	23[3]	28[4]
Units: Proportion of Patients				
number (confidence interval 95%)	0.00 (0.000 to 0.143)	0.042 (0.007 to 0.202)	0.087 (0.024 to 0.268)	0.071 (0.020 to 0.226)

Notes:

[1] - RS-NRI

[2] - RS-NRI

[3] - RS-NRI
[4] - RS-NRI

Statistical analyses

Statistical analysis title	Unadjusted absolute risk differences to placebo
Statistical analysis description: [Treatment - Placebo]. 95% CI for risk difference were calculated using the method of Newcombe.	
Comparison groups	Placebo v 300 mg Spesolimab (BI 655130) SD
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.105
upper limit	0.202

Statistical analysis title	Unadjusted absolute risk differences to placebo
Statistical analysis description: [Treatment - Placebo]. 95% CI for risk difference were calculated using the method of Newcombe.	
Comparison groups	Placebo v 450 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.268

Statistical analysis title	Unadjusted absolute risk differences to placebo
Statistical analysis description: [Treatment - Placebo]. 95% CI for risk difference were calculated using the method of Newcombe.	
Comparison groups	Placebo v 1200 mg Spesolimab (BI 655130) q4w

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	0.226

Secondary: Proportion of patients with Clinical Response at week 12

End point title	Proportion of patients with Clinical Response at week 12

End point description:

Proportion of patients with Clinical Response (defined as Rectal Bleeding Score (RBS) ≤ 1 or decrease by ≥1 from
baseline; and total Mayo Clinical Score (MCS) decrease by ≥ 3 and 30% from baseline) at week 12.
Proportion of patients is calculated as n/N, with n=number of patients with clinical response at week 12 and N=number of patients analyzed. 95% Confidence Intervalls (CI) are calculated using the method of Wilson.

Randomised Set - Non Response Imputation (RS-NRI): The randomised set included all randomised patients, including patients with non-response imputation.

End point type	Secondary

End point timeframe:

At week 12.

End point values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w	1200 mg Spesolimab (BI 655130) q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[5]	24[6]	23[7]	28[8]
Units: Proportion of participants				
number (confidence interval 95%)	0.217 (0.097 to 0.419)	0.167 (0.067 to 0.359)	0.261 (0.125 to 0.465)	0.250 (0.127 to 0.434)

Notes:

[5] - RS-NRI

[6] - RS-NRI

[7] - RS-NRI

[8] - RS-NRI

Statistical analyses

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 300 mg Spesolimab (BI 655130) SD

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.276
upper limit	0.176

Statistical analysis title	Unadjusted absolute risk difference to placebo
Statistical analysis description: [Treatment - Placebo]. 95% CI for risk difference were calculated using the method of Newcombe.	
Comparison groups	Placebo v 450 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.199
upper limit	0.28

Statistical analysis title	Unadjusted absolute risk difference to placebo
Statistical analysis description: [Treatment - Placebo]. 95% CI for risk difference were calculated using the method of Newcombe.	
Comparison groups	Placebo v 1200 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.252

Secondary: Proportion of patients with Endoscopic Improvement at week 12

End point title	Proportion of patients with Endoscopic Improvement at week 12

End point description:

Proportion of patients with Endoscopic Improvement at week 12 (defined as modified Endoscopic Subscore (mESS) ≤ 1)
Proportion of patients was calculated as n/N, with n=number of patients with Endoscopic Improvment at Week 12 and N=number analysed. 95% Confidence Intervalls (CI) were calculated using the method of Wilson.

Randomised Set - Non Response Imputation (RS-NRI): The randomised set included all randomised patients, including patients with non-response imputation.

End point type	Secondary

End point timeframe:

At week 12.

End point values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w	1200 mg Spesolimab (BI 655130) q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[9]	24[10]	23[11]	28[12]
Units: Proportion of patients				
number (confidence interval 95%)	0.000 (0.000 to 0.143)	0.083 (0.023 to 0.258)	0.087 (0.024 to 0.268)	0.071 (0.020 to 0.226)

Notes:

[9] - RS-NRI

[10] - RS-NRI

[11] - RS-NRI

[12] - RS-NRI

Statistical analyses

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 300 mg Spesolimab (BI 655130) SD
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	0.258

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].

95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 1200 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.081
upper limit	0.226

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 450 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.268

Secondary: Proportion of patients with combined Endoscopic Improvement and Histologic Remission at week 12

End point title	Proportion of patients with combined Endoscopic Improvement and Histologic Remission at week 12

End point description:

Proportion of patients with combined Endoscopic Improvement and histologic remission at week 12 (defined as modified Endoscopic Subscore (mESS) ≤ 1 and Robarts Histology Index ≤ 6). Proportion of patients was calculated as n/N, with n= number of patients with Endoscopic Improvement and histologic remission at week 12 and N=number of patients analysed.

Randomised Set - Non Response Imputation (RS-NRI): The randomised set included all randomised patients, including patients with non-response imputation.

End point type	Secondary

End point timeframe:

At week 12.

End point values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w	1200 mg Spesolimab (BI 655130) q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[13]	24[14]	23[15]	28[16]
Units: Proportion of patients				
number (confidence interval 95%)	0.00 (0.000 to 0.143)	0.083 (0.023 to 0.258)	0.043 (0.008 to 0.210)	0.036 (0.006 to 0.177)

Notes:

[13] - RS-NRI

[14] - RS-NRI

[15] - RS-NRI

[16] - RS-NRI

Statistical analyses

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 300 mg Spesolimab (BI 655130) SD
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	0.258

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 450 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.21

Statistical analysis title	Unadjusted absolute risk difference to placebo

Statistical analysis description:

[Treatment - Placebo].
95% CI for risk difference were calculated using the method of Newcombe.

Comparison groups	Placebo v 1200 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.177

Secondary: Change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline at week 12

End point title	Change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline at week 12

End point description:

Change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline at Week 12.
The IBDQ is a 32-item self-report questionnaire for patients with IBD to evaluate the patient reported outcomes across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). The response options describe the magnitude or frequency of impairment from 1 (most severe) to 7 (no impairment). The items are summed up, resulting in a sum score ranging from 32 to 224 points, with higher scores indicating better outcomes. A score change of 16 is reported to reflect the minimal clinically important difference (MCID).

Mean is adjusted mean.

Modified Randomised Set (m-RS): The m-RS included all patients in the RS who had a baseline and at least 1 post-baseline
measurement for the endpoint under consideration.

End point type	Secondary

End point timeframe:

Assessed: At baseline, week 2, 4, 8 and week 12. Reported: From baseline to week 12.

End point values	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w	1200 mg Spesolimab (BI 655130) q4w
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[17]	19[18]	21[19]	18[20]
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	19.8 (4.7 to 35.0)	19.5 (4.6 to 34.5)	21.2 (6.6 to 35.9)	20.8 (6.3 to 35.4)

Notes:

[17] - m-RS

[18] - m-RS

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Statistical analyses

Statistical analysis title	Mixed model analysis

Statistical analysis description:

Restricted maximum likelihood (REML)-based repeated measures approach. The model included fixed, categorical effects of treatment, visit, and treatment by visit interaction, and stratification factors (prior biologic treatment failure and concomitant corticosteroid therapy at Visit 2/randomisation), as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo v 300 mg Spesolimab (BI 655130) SD
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9776
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.6
upper limit	21
Variability estimate	Standard error of the mean
Dispersion value	10.7

Statistical analysis title	Mixed model approach

Statistical analysis description:

Restricted maximum likelihood (REML)-based repeated measures approach. The model included fixed, categorical effects of treatment, visit, and treatment by visit interaction, and stratification factors (prior biologic treatment failure and concomitant corticosteroid therapy at Visit 2/randomisation), as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo v 450 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.894
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.6
upper limit	22.4

Variability estimate	Standard error of the mean
Dispersion value	10.6

Statistical analysis title	Mixed model approach

Statistical analysis description:

Restricted maximum likelihood (REML)-based repeated measures approach. The model included fixed, categorical effects of treatment, visit, and treatment by visit interaction, and stratification factors (prior biologic treatment failure and concomitant corticosteroid therapy at Visit 2/randomisation), as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. An unstructured covariance structure was used to model the within-patient measurements

Comparison groups	Placebo v 1200 mg Spesolimab (BI 655130) q4w
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9241
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	22.1
Variability estimate	Standard error of the mean
Dispersion value	10.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening until end of study, up to 29 weeks.

Adverse event reporting additional description:

Safety Analysis Set (SAF): All patients who were randomised and received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

A solution of placebo was administered as intravenous infusion once every 4 weeks over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Reporting group title	300 mg Spesolimab (BI 655130) SD

Reporting group description:

A single dose (SD) of 300 milligram (mg) solution of spesolimab was administered as intravenous infusion at week 0 in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Reporting group title	450 mg Spesolimab (BI 655130) q4w

Reporting group description:

450 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Reporting group title	1200 mg Spesolimab (BI 655130) q4w

Reporting group description:

1200 mg solution of spesolimab was administered, as intravenous infusion, once every 4 weeks (q4w) over a period of 12 weeks, (at week 0, week 4, week 8) in patients with moderate to severe ulcerative colitis who had failed previous biological treatments in the past.

Serious adverse events	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)	3 / 24 (12.50%)	2 / 23 (8.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 23 (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
Infusion related reaction			

subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 23 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 23 (4.35%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 23 (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

Serious adverse events	1200 mg Spesolimab (BI 655130) q4w		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	300 mg Spesolimab (BI 655130) SD	450 mg Spesolimab (BI 655130) q4w
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)	7 / 24 (29.17%)	7 / 23 (30.43%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 23 (0.00%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 23 (21.74%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	6	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	4
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Colitis ulcerative			
subjects affected / exposed	0 / 23 (0.00%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	2 / 23 (8.70%)
occurrences (all)	0	1	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	2 / 24 (8.33%)	2 / 23 (8.70%)
occurrences (all)	0	2	3

Non-serious adverse events	1200 mg Spesolimab (BI 655130) q4w		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 27 (62.96%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
General disorders and administration			

site conditions Fatigue subjects affected / exposed occurrences (all) Feeling hot subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 3 0 / 27 (0.00%) 0		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Colitis ulcerative subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 6 / 27 (22.22%) 6 2 / 27 (7.41%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 3		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0 2 / 27 (7.41%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2		
Infections and infestations			

Herpes zoster subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2018	Global amendment 2 was implemented after approval by the competent authority and IEC or IRB. The following main changes to the CTP were introduced by this amendment a:ddition of the further endpoints "proportion of patients with Complete Remission at Week 12" and "proportion of patients with Endoscopic Remission at Week 12"; inclusion criterion #3 was updated with regard to the definition of moderate to severe activity; inclusion criterion #5 was updated to add the requirement of documentation for past inadequate response or loss of response; inclusion criterion #6 and the restrictions were updated to allow the use of prednisone or equivalent and of oral beclomethasone dipropionate for the treatment of UC as well as the short-term use of systemic corticosteroids for the treatment of AEs; inclusion criterion #8 and the restrictions for women of childbearing potential and male participants were updated to align with updated contraception requirements in the Investigator's Brochure (IB); exclusion criterion #9 was updated with regard to the required time window of faecal transplant; exclusion criterion #12 was updated with regard to active tuberculosis and the details for the required TB testing; in the study definitions, surgical procedure was added to the rescue treatments; some of the exclusion criteria were aligned with project definitions and the IB update; cytokine release syndrome was deleted from the list of AESIs.
17 December 2018	This amendment was necessary to implement changes (some of which were requested by Health Authorities) prior to the initial approval and start of the trial. The following main changes to the CTP were introduced by this amendment: The definition of hepatic injury was changed following a request from the FDA; a stopping rule related to a hepatic injury alert without identification of an alternative cause was added; in exclusion criterion #16 relating to pathological safety lab parameters, the threshold for the minimal haemoglobin level was increased based on FDA recommendation; exemptions from the SAE reporting were removed.

09 October 2019	The following main changes to the CTP were introduced by this amendment: the option to measure drug levels of previous biologics to shorten the washout period to less than 8 weeks was introduced; restrictions regarding previous and concomitant treatment were updated; exclusion criterion #14 was updated with regard to the required time window for remote history of malignancy; exclusion criterion #5 was updated to further specify that the positive stool examination for Clostridium difficile corresponded to a positive toxin A/B test. Investigators and other site personnel were informed upfront (dated 29 Apr 2019); the AESI "Infusion reactions including anaphylactic reaction" was renamed to "Systemic hypersensitivity including infusion reaction and anaphylactic reaction" to align the terminology with project standards; the AE collection definition was updated for patients rolling over into the open-label extension trial to ensure that any AE reported prior to the first dosing in the extension trial was assigned to trial 1368-0005; in the case of rescheduled visits, the calculation of subsequent visits was changed from the date of the previous visit to Day 0; it was clarified that the recommendation to perform a PPD skin test in the case of undetermined re-test results of the QuantiFERON®-TB test applied for Screening and the EOS Visit; because of premature termination of recruitment, none of the patients was randomised after Global amendment 3 had been implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to recruitment issues during phase II, the trial was prematurely ended, according to a protocol defined option. Phase III was not conducted. The trial was completed as defined in the protocol.

Notes: