



Clinical trial results: Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease

Summary

EudraCT number	2017-003090-34
Trial protocol	AT BE DE NL HU DK
Global end of trial date	04 July 2022

Results information

Result version number	v1 (current)
This version publication date	16 July 2023
First version publication date	16 July 2023

Trial information

Trial identification

Sponsor protocol code	1368-0008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03752970
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim , Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim , Call Center, Boehringer Ingelheim, 001 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	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2021
Global end of trial reached?	Yes
Global end of trial date	04 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the pathomechanisms involved in the generation and healing of Crohn's disease associated perianal fistulas. To understand the mode of action (MoA) of spesolimab in patients with Crohn's disease and draining perianal fistulas.

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 subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2019
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: 4
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	28
EEA total number of subjects	27

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)	28
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening Cohort did not receive study treatment.

Study Cohort was a randomised, double-blind, placebo-controlled, Phase IIa design, in 2 periods each of 12 weeks' duration. Patients who had clinical benefit were offered continued treatment in an open label, long-term extension study. Patients who did not continue were followed up at Week 36.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

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:

Screening Cohort was non-randomised and not blinded.

Study Cohort was randomised and double blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Screening Cohort

Arm description:

Patients enrolled in the Screening Cohort did not receive study treatment. This was a feasibility phase for fistula preparation and seton placement to determine the tissue samples that were suitable for analysis of the primary endpoint in the Study Cohort.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Study Cohort - Placebo
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Arm description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). At week 12 achievement of combined perianal fistula remission was determined, patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20). Patients with combined perianal fistula remission remained on Placebo and were treated with placebo intravenously every 4 weeks (week 12, 16 and 20).

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:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). At week 12 achievement of combined perianal fistula remission was determined, patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20). Patients with combined perianal fistula remission remained on Placebo and were treated with placebo intravenously every 4 weeks (week 12, 16 and 20).

Arm title	Study Cohort - Spesolimab
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Arm description:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). At week 12 Placebo patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20).

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:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). At week 12 Placebo patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20).

Number of subjects in period 1 ^[1]	Screening Cohort	Study Cohort - Placebo	Study Cohort - Spesolimab
Started	6	10	11
Completed	6	9	8
Not completed	0	1	3
Consent withdrawn by subject	-	-	2
Lost to follow-up	-	-	1
Lack of efficacy	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 28 subjects enrolled, 27 subjects were entered.

Baseline characteristics

Reporting groups

Reporting group title	Screening Cohort
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Reporting group description:

Patients enrolled in the Screening Cohort did not receive study treatment. This was a feasibility phase for fistula preparation and seton placement to determine the tissue samples that were suitable for analysis of the primary endpoint in the Study Cohort.

Reporting group title	Study Cohort - Placebo
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). At week 12 achievement of combined perianal fistula remission was determined, patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20). Patients with combined perianal fistula remission remained on Placebo and were treated with placebo intravenously every 4 weeks (week 12, 16 and 20).

Reporting group title	Study Cohort - Spesolimab
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). At week 12 Placebo patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20).

Reporting group values	Screening Cohort	Study Cohort - Placebo	Study Cohort - Spesolimab
Number of subjects	6	10	11
Age categorical			
All subjects who entered the Screening Cohort or the Study Cohort.			
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)	6	10	11
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: years			
arithmetic mean	42.5	34.0	39.2
standard deviation	± 10.8	± 8.3	± 10.8
Sex: Female, Male			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Participants			
Female	4	3	2
Male	2	7	9
Race (NIH/OMB)			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Subjects			

American Indian or Alaska Native	0	0	0
Asian	0	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	6	8	10
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	10	11
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	27		
Age categorial			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	27		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Participants			
Female	9		
Male	18		
Race (NIH/OMB)			
All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	24		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			

All subjects who entered the Screening Cohort or the Study Cohort.			
Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	27		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Screening Cohort
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Reporting group description:

Patients enrolled in the Screening Cohort did not receive study treatment. This was a feasibility phase for fistula preparation and seton placement to determine the tissue samples that were suitable for analysis of the primary endpoint in the Study Cohort.

Reporting group title	Study Cohort - Placebo
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). At week 12 achievement of combined perianal fistula remission was determined, patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20). Patients with combined perianal fistula remission remained on Placebo and were treated with placebo intravenously every 4 weeks (week 12, 16 and 20).

Reporting group title	Study Cohort - Spesolimab
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). At week 12 Placebo patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20).

Primary: The total number of deregulated genes at Week 4

End point title	The total number of deregulated genes at Week 4 ^{[1][2]}
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End point description:

The total number of deregulated genes based on biopsies from the inner fistula orifice at Week 4 comparing changes in gene expression from baseline between the two treatment groups. For each gene, a repeated measures linear regression model was utilized with treatment, visit (baseline, week 4), treatment by visit interaction as fixed effect and patient as a blocking factor.

Changes were quantified by log₂ fold changes (FC) and associated False Discovery Rate (FDR) adjusted p-values.

Genes will be considered deregulated if they fulfil the following criteria:

- FDR adjusted p-value ≤ 0.05
- $|\text{fold change}| \geq 1.5$ ($|\log_2 \text{fold change}| \geq 0.58$)

RNA Sequencing Set: All patients who were randomised and treated with any amount of study drug and who provide a valid baseline and at least one valid post-baseline observation for at least one gene expression variable of biopsy. Data analysed with original results (OR) approach, implying the presentation of data exactly as observed.

End point type	Primary
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End point timeframe:

Biopsies taken at screening (Week -3) and at week 4 of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses was performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As stated in the SAP and Protocol, the endpoint was only planned to be analyzed for the Study Cohort.

End point values	Study Cohort - Placebo	Study Cohort - Spesolimab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: Deregulated genes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with perianal fistula response at Week 12

End point title	Number of patients with perianal fistula response at Week 12 ^[3]
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End point description:

Number of patients with perianal fistula response at Week 12 defined as closure of at least 50% of external openings, no drainage/discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas.

Includes all patients of the Study Cohort who provided a baseline value and at least one post-baseline value for at least one secondary endpoint or further efficacy endpoint. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned to at randomisation. The no response imputation (NRI) approach is applied: missing visits were imputed whereby all subsequent visits after a patient took rescue medication for the disease under study or died due to any cause were considered to be missing..

End point type	Secondary
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End point timeframe:

At baseline (day 1) and week 12 (day 85) of treatment.

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analyses was performed.

End point values	Study Cohort - Placebo	Study Cohort - Spesolimab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Participants	7	1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Study Cohort - Placebo v Study Cohort - Spesolimab
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.609

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.186

Secondary: Number of patients with perianal fistula remission at Week 12

End point title	Number of patients with perianal fistula remission at Week 12 ^[4]
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End point description:

Proportion of patients with perianal fistula remission at Week 12 defined as closure of all external openings, no drainage/discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas.

Includes all patients of the Study Cohort who provided a baseline value and at least one post-baseline value for at least one secondary endpoint or further efficacy endpoint. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned to at randomisation. The no response imputation (NRI) approach is applied: missing visits were imputed whereby all subsequent visits after a patient took rescue medication for the disease under study or died due to any cause were considered to be missing.

End point type	Secondary
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End point timeframe:

At baseline (day 1) and week 12 (day 85) of treatment.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As stated in the SAP and Protocol, the endpoint was only planned to be analyzed for the Study Cohort.

End point values	Study Cohort - Placebo	Study Cohort - Spesolimab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Participants	6	1		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Study Cohort - Placebo v Study Cohort - Spesolimab
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.509
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.816
upper limit	-0.087

Secondary: Number of patients with combined perianal fistula remission at Week 12

End point title	Number of patients with combined perianal fistula remission at Week 12 ^[5]
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End point description:

Number of patients with combined perianal fistula remission at Week 12 defined as closure of all external openings, no drainage/discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas, AND absence collections of >2 centimeter, confirmed by magnetic resonance imaging (MRI) in at least 2 of 3 dimensions – blinded and centrally read.

Includes all patients of the Study Cohort who provided a baseline value and at least one post-baseline value for at least one secondary endpoint or further efficacy endpoint. Following the intent-to-treat principle, patients will be analysed according to the treatment they were assigned to at randomisation. The no response imputation (NRI) approach is applied: missing visits were imputed whereby all subsequent visits after a patient took rescue medication for the disease under study or died due to any cause were considered to be missing.

End point type	Secondary
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End point timeframe:

At baseline (day 1) and week 12 (day 85) of treatment.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As stated in the SAP and Protocol, the endpoint was only planned to be analyzed for the Study Cohort.

End point values	Study Cohort - Placebo	Study Cohort - Spesolimab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Participants	6	1		

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Study Cohort - Placebo v Study Cohort - Spesolimab
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	-0.509
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.816
upper limit	-0.087

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening cohort: up to 56 days.

Period 1: from treatment start in period 1 till start in period 2, up to 84 days.

Period 2: from treatment start in period 2 till end of last infusion in period 2 + residual effect period of 112 days, up to 182 days.

Adverse event reporting additional description:

Screening cohort: all patients of the Screening Cohort who entered the trial.

Study cohort: all patients who were randomised and treated with any amount of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Study Cohort period 2: Placebo - Spesolimab
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). At week 12 achievement of combined perianal fistula remission was determined, patients without combined perianal fistula remission were switched to spesolimab and were treated with spesolimab 1200 milligram intravenously every 4 weeks (week 12, 16 and 20). The arm only considers adverse events reported in period 2.

Reporting group title	Study Cohort period 2: Spesolimab - Spesolimab
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). The arm only considers adverse events reported in period 2

Reporting group title	Study Cohort period 2: Placebo - Placebo
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8, 12, 16 and 20). The arm only considers adverse events reported in period 2.

Reporting group title	Study Cohort period 1: Placebo
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Placebo intravenously every 4 weeks (week 0, 4, 8). The arm only considers adverse events reported in period 1.

Reporting group title	Study Cohort period 1: Spesolimab
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Reporting group description:

Patients with perianal fistulising Crohn's disease received Spesolimab 1200 milligram intravenously every 4 weeks (week 0, 4, 8). The arm only considers adverse events reported in period 1.

Reporting group title	Screening cohort
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Reporting group description:

Patients enrolled in the Screening Cohort did not receive study treatment. This was a feasibility phase for fistula preparation and seton placement to determine the tissue samples that were suitable for analysis of the primary endpoint in the Study Cohort.

Serious adverse events	Study Cohort period 2: Placebo - Spesolimab	Study Cohort period 2: Spesolimab - Spesolimab	Study Cohort period 2: Placebo - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 5 (20.00%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 5 (20.00%)
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			
Proctalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	0 / 5 (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			
Peritonsillar abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Study Cohort period 1: Placebo	Study Cohort period 1: Spesolimab	Screening cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (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
Infections and infestations			
Peritonsillar abscess			

subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (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

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

Non-serious adverse events	Study Cohort period 2: Placebo - Spesolimab	Study Cohort period 2: Spesolimab - Spesolimab	Study Cohort period 2: Placebo - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 9 (55.56%)	3 / 5 (60.00%)
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Enanthema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 9 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 9 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 9 (11.11%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Anal fissure subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Crohn's disease subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Anal fistula subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	1 / 5 (20.00%) 1
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Skin and subcutaneous tissue disorders Rash maculo-papular			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	1 / 5 (20.00%) 1
Arthropathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Rheumatic disorder subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 5 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Infections and infestations Anal abscess subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	1 / 5 (20.00%) 1
Abscess limb subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Asymptomatic COVID-19			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 9 (0.00%) 0	1 / 5 (20.00%) 1
Bronchitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Clostridium difficile infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 5 (0.00%) 0
Latent tuberculosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 5 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 5 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 9 (11.11%) 1	0 / 5 (0.00%) 0
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 9 (0.00%) 0	0 / 5 (0.00%) 0

Non-serious adverse events	Study Cohort period 1: Placebo	Study Cohort period 1: Spesolimab	Screening cohort
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 10 (90.00%)	6 / 11 (54.55%)	1 / 6 (16.67%)
Vascular disorders Raynaud's phenomenon subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
General disorders and administration site conditions			

Enanthema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Anal fissure subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Crohn's disease subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Anal fistula subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Endocrine disorders Goitre subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0

Arthropathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rheumatic disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Abscess limb			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Asymptomatic COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Latent tuberculosis			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	3 / 11 (27.27%) 3	0 / 6 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	0 / 6 (0.00%) 0
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	0 / 6 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2019	<ul style="list-style-type: none">- The outcome of the Screening Cohort was added, and the samples required during fistula preparation visits were clarified- Screening of patients for the Study Cohort was extended because a minimum of approximately 15 patients with valid baseline and post treatment biopsies were needed for primary endpoint analysis- Crohn's disease activity index clinical response was updated according to standards in the indication Crohn's disease (CD)- Fistula relapse was added as a further endpoint, based on expert recommendation- Endoscopy at Visit 9, and requirements for Adverse Events (AE) reporting was amended for harmonisation with requirements in study 1368-0007- The visit window for Visit 9 was extended to 7 days for flexibility of scheduling investigations- The wording of instructions for steroid tapering was amended for flexibility
02 April 2020	<ul style="list-style-type: none">- Adjustments were made to some of the inclusion and exclusion criteria, and to visit windows, to facilitate screening visits, reduce the burden on patients, and to improve recruitment. Changes were made to variables that would not affect primary or secondary endpoint analysis- The number of sites was increased- Ileocolonoscopy at baseline, and Visits 6 and 9 ceased to be mandatory. Recto- or proctoscopy was required instead- Definitions for perianal fistula activity were amended to clarify that assessments were performed by investigators at the study sites. Central reading was used for efficacy assessments- The bioanalytical laboratory received the randomisation code to avoid unnecessary testing of samples for Pharmacokinetic (PK) and Anti-drug antibodies (ADA) from patients who received placebo- A staged approach for biomarker sample analysis was introduced due to the exploratory nature of the mechanism under test and the timing of effect on candidate biomarkers in the study
23 October 2020	<ul style="list-style-type: none">- The interim analysis was added- Description of the development programme of spesolimab was updated following the decision by BI to discontinue development of the drug in ulcerative colitis. The decision was based on efficacy results, which showed a lower than expected efficacy of clinical endpoints. The decision was not related to, or triggered by, any safety findings- The requirement to remove seton drainage 2 weeks before the first surgical visit was removed to improve feasibility of the trial. Fistulas had to be actively draining to protect the primary endpoint analysis- It was clarified that surgical procedures to treat fistulas (except for seton drainage) was not allowed after randomisation. At the time this amendment was implemented, fistula repair had already been performed on 2 patients, which, therefore, were not reported as Important protocol deviations- Exclusion criterion 10 was amended to allow patients to continue pre-existing anti-tumour necrosis factor (TNF) treatment. Discontinuation of anti-TNF therapy was not possible for most of the target population because of the need to ensure controlled luminal activity throughout the study- Peri-operative antibiotics were permitted on the day before until the day after fistula preparation visits, if required according to standard of care- The benefit-risk section was updated to add an assessment of the effect of the COVID-19 pandemic on patients receiving spesolimab. It was concluded that there was no additional risk. However, challenges due to the pandemic were acknowledged, including restrictions on physical visits to study sites. Therefore, flexibility was added to allow administration of trial medication at the patient's home, if acceptable according to local law and regulations

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.

For the primary endpoint, due to the limited number of evaluable samples from the curettage at baseline and at Week 4, curettage biopsies were not included in the gene expression analysis.

Notes: