Clinical trial results:
Exploratory trial to assess mechanism of action, clinical effect, safety and tolerability of 12 weeks of treatment with BI 655130 in patients with active ulcerative colitis (UC)

Summary

EudraCT number	2017-000100-20
Trial protocol	DE GB BE
Global end of trial date	24 October 2019

Results information

Result version number	v3 (current)
This version publication date	24 September 2021
First version publication date	07 November 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1368-0004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03100864
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany,
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	30 March 2020

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to understand the mode of action of spesolimab in patients with active ulcerative colitis.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2017
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	Germany: 11
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	17
EEA total number of subjects	15

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)	15
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an Phase IIa multi-centre, non-randomised, uncontrolled single arm, open-label, exploratory trial to assess biomarker changes in response to Interleukin-36 signalling blockade induced by treatment with spesolimab in patients with moderate to severe active Ulcerative colitis.

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	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label, single-arm trial.

Arms

Arm title	Spesolimab 1200 mg Intravenous (i.v.)

Arm description:

1200 milligram Spesolimab (infusion solution, BI 655130) was given for 12 weeks intravenously with a concentration of 20 milligram/milliliter every four weeks (on Day 1, Week 4, and Week 8).

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	BI 655130
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 milligram Spesolimab (infusion solution, BI 655130) was given for 12 weeks intravenously with a concentration of 20 milligram/milliliter every four weeks (on Day 1, Week 4, and Week 8).

Number of subjects in period 1[1]	Spesolimab 1200 mg Intravenous (i.v.)
Started	8
Completed	8

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 enrolled subjects, 8 were treated

Baseline characteristics

Reporting groups	
Reporting group title	Spesolimab 1200 mg Intravenous (i.v.)
Reporting group description:	
1200 milligram Spesolimab (infusion solution, BI 655130) was given for 12 weeks intravenously with a concentration of 20 milligram/milliliter every four weeks (on Day 1, Week 4, and Week 8).	

Reporting group values	Spesolimab 1200 mg Intravenous (i.v.)	Total	
Number of subjects	8	8	
Age categorical			
Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.			
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)	7	7	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous			
Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.			
Units: years			
arithmetic mean	43.1		
standard deviation	± 19.1	-	
Sex: Female, Male			
Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.			
Units: Participants			
Female	3	3	
Male	5	5	
Race (NIH/OMB)			
Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	

Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	8	8	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	8	8	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Spesolimab 1200 mg Intravenous (i.v.)

Reporting group description:

1200 milligram Spesolimab (infusion solution, BI 655130) was given for 12 weeks intravenously with a concentration of 20 milligram/milliliter every four weeks (on Day 1, Week 4, and Week 8).

Primary: The total number of deregulated genes comparing baseline to post treatment, analysed by gene expression of mucosal biopsies via RNA sequencing, per time point up to Week 12

End point title	The total number of deregulated genes comparing baseline to post treatment, analysed by gene expression of mucosal biopsies via RNA sequencing, per time point up to Week 12[1]

End point description:

The total number of deregulated genes comparing baseline to post treatment, analysed by gene expression of mucosal biopsies via RNA sequencing, per time point up to Week 12. A total of 60,675 genes were evaluated, 40,586 genes were included in the differential expression analyses. Based on the raw read count values the DESeq2 method, one of the standard methods to analyse RNAseq data, was used for the gene expression analysis and to identify deregulated genes. A gene was considered deregulated with a FDR (false discovery rate) adjusted p-value < 0.01 and a fold change ≤ -1.3 or ≥ 1.3.

Completers analysis set (CAS): completed the trial medication through to end of trial visit, had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.

End point type	Primary

End point timeframe:

Measurements done at baseline (day -8 to -6), day 1, day 4, day 15, day 57 and day 85 (week 12).

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	5[2]			
Units: Deregulated genes				
Change from baseline to Day 1	3			
Change from baseline to Day 4	5			
Change from baseline to Day 15 (week 2)	2			
Change from baseline to Day 57 (week 8)	7			
Change from baseline to Day 85 (week 12)	9			

Notes:

[2] - CAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in C-reactive protein (CRP) from baseline to Week 12

End point title	Percent change in C-reactive protein (CRP) from baseline to Week 12

End point description:

Percent change in C-reactive protein (CRP) from baseline to Week 12 (day 85).

Safety analysis set (SAF): This patient set included all entered patients who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Measurements done at baseline (day -8 to -6) and week 12 (day 85).

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	5[3]			
Units: percentage change (%)				
median (full range (min-max))	-79.6 (-97.9 to 936.7)			

Notes:

[3] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in faecal calprotectin from baseline to Week 12

End point title	Percent change in faecal calprotectin from baseline to Week 12

End point description:

Percent change in faecal calprotectin from baseline to week 12 (day 85).

Safety analysis set (SAF): This patient set included all entered patients who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Measurements done at baseline (day -8 to -6) and week 12 (day 85).

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	5[4]			
Units: percentage change (%)				
median (full range (min-max))	13.0 (-98.7 to			

	219.3)

Notes:

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in faecal lactoferrin from baseline to Week 12

End point title	Percent change in faecal lactoferrin from baseline to Week 12

End point description:

Percent change in faecal lactoferrin from baseline to week 12 (day 85).

Safety analysis set (SAF): This patient set included all entered patients who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Measurements done at baseline (day -8 to -6) and week 12 (day 85).

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	5[5]			
Units: percentage change (%)				
median (full range (min-max))	0.4 (-99.7 to 388.7)			

Notes:

[5] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical remission (defined as Mayo score ≤2 points, and all subscores ≤1 point) at Week 12

End point title	Number of participants with clinical remission (defined as Mayo score ≤2 points, and all subscores ≤1 point) at Week 12

End point description:

Number of participants with clinical remission (defined as Mayo score ≤2 points, and all subscores ≤1 point) at Week 12. The Mayo score is a composite disease activity score consisting of 4 items or subscores: stool frequency (relative to normal), rectal bleeding, physician’s global assessment (PGA), and endoscopic appearance. The overall range of the Mayo score was 0 to 12 (higher scores being worse) and each subscore had a range of 0 to 3.

Full analysis set (FAS): patients who received at least 1 dose of study drug, who had a baseline and at least 1 post baseline measurement for any clinical efficacy or biomarker endpoint without any Important protocol deviation flagged for exclusion or rescue use on or after Visit 1b but prior to administration of the first dose of spesolimab.

End point type	Secondary

End point timeframe:

Week 12 (day 85) following start of treatment.

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	5[6]			
Units: Participants				
number (confidence interval 95%)	0 (0.000 to 0.434)			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with drug related adverse events (AEs)

End point title	Number of patients with drug related adverse events (AEs)

End point description:

Number of patients with drug related adverse events (AEs) during the on-treatment period.

Safety analysis set (SAF): This patient set included all entered patients who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Date of start of infusion of first study drug (Day 1) till the date of end of infusion of last study drug (day 57) + 140 days at 11:59 p.m., up to 197 days.

End point values	Spesolimab 1200 mg Intravenous (i.v.)			
Subject group type	Reporting group			
Number of subjects analysed	8[7]			
Units: Participants				
Number of patients with drug related AEs	6			

Notes:

[7] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of start of infusion of first study drug (Day 1) till the date of end of infusion of last study drug (day 57) + 140 days at 11:59 p.m., up to 197 days.

Adverse event reporting additional description:

Safety analysis set (SAF): This patient set included all entered patients who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Spesolimab 1200 mg Intravenous (i.v.)

Reporting group description:

1200 milligram Spesolimab (infusion solution, BI 655130) was given for 12 weeks intravenously with a concentration of 20 milligram/milliliter every four weeks (on Day 1, Week 4, and Week 8).

Serious adverse events	Spesolimab 1200 mg Intravenous (i.v.)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Spesolimab 1200 mg Intravenous (i.v.)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Amylase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Eye inflammation			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
General disorders and administration			

site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Colitis ulcerative subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Skin and subcutaneous tissue disorders Rash macular subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 2 1 / 8 (12.50%) 2		

Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2018	Global Amendment 1: - Safety information and PK modelling were updated with data from trials 1368.1 and 1368.2. As a result of these changes, the lower body weight limit of 60 kg was deleted as it was no longer required - Sigmoidoscopy at 4 hours after the first i.v. infusion was deleted to reduce the overall number of sigmoidoscopies in the trial. All biopsy samples had to be obtained prior to trial treatment administration - The trial design was updated to add the option of long-term treatment in trial 1368-0017 for patients who completed 12 weeks of treatment in this exploratory trial - The trial population was extended to patients who had been previously treated with TNF antagonist(s) but who did not stop that treatment due to primary non-response or lack of response. This change was made to facilitate recruitment. The last dose of TNF antagonist(s) had to be at least 8 weeks or 3 half-lives (whichever was longer) from screening - Further guidance to investigators was added regarding infusion reactions, CRS and infections - Infusion reactions including anaphylactic reactions, CRS and opportunistic and Mycobacterium tuberculosis infections were added to AESIs for consistency across the spesolimab programme - The section on equivalent doses of corticosteroids was updated to add budesonide and to remove 16-methylprednisolone
18 May 2018	Global Amendment 2: - Following feedback from experts, the deletion of sigmoidoscopy with biopsy sample collection and blood sampling for gene expression and methylation pattern analysis at 4 hours after the first i.v. infusion (Amendment 1) was reversed and was re-included in the trial - Additional study sites were planned to be included
03 April 2019	Global Amendment 3: - The upper age limit was increased from 65 years to 75 years to facilitate recruitment and for consistency with more recent trials in the programme

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported