Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence

Summary

EudraCT number	2019-000886-19
Trial protocol	FR DE GB AT NL
Global end of trial date	25 August 2022

Results information

Result version number	v1 (current)
This version publication date	27 August 2023
First version publication date	27 August 2023

Trial information

Trial identification

Sponsor protocol code	TAK-018-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03943446
WHO universal trial number (UTN)	U1111-1225-5064

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	95 Hayden Avenue, Lexington, Massachusetts, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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	25 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main aim is to evaluate the efficacy of TAK-018 in reducing endoscopic recurrence of intestinal inflammation in postoperative participants with CD after planned laparoscopic ileocecal resection with primary anastomosis.

Protection of trial subjects:

Each subject signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	34
EEA total number of subjects	23

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)	31

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 18 investigative sites in the United States, Australia, Germany, France and United Kingdom from 4 August 2020 to 25 August 2022.

Pre-assignment

Screening details:

Participants with Crohn’s disease (CD) who had undergone a planned laparoscopic ileocecal resection received TAK-018 for prevention of the recurrence of postoperative CD. The participants were randomized in 1:1:1 ratio to three treatment groups i.e. TAK-018 low dose, TAK-018 high dose, or placebo for a 26-week treatment period.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

TAK-018 placebo-matching tablets, orally, twice daily (BID) for up to 27.7 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-018 placebo-matching tablets.

Arm title	TAK-018 0.30 g Low Dose

Arm description:

TAK-018 0.30 g, tablets, orally, BID for up to 31.7 weeks.

Arm type	Experimental
Investigational medicinal product name	TAK-018
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-018 0.30 g tablets.

Arm title	TAK-018 1.5 g High Dose

Arm description:

TAK-018 1.5 g, tablets, orally, BID for up to 26.1 weeks.

Arm type	Experimental

Investigational medicinal product name	TAK-018
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-018 1.5 g tablets.

Number of subjects in period 1	Placebo	TAK-018 0.30 g Low Dose	TAK-018 1.5 g High Dose
Started	12	11	11
Pharmacokinetic (PK) analysis set	12	11	11
Completed	5	7	4
Not completed	7	4	7
Consent withdrawn by subject	1	1	2
Study Terminated by Sponsor	1	2	1
Lost to follow-up	-	-	1
Reason not Specified	5	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
TAK-018 placebo-matching tablets, orally, twice daily (BID) for up to 27.7 weeks.	
Reporting group title	TAK-018 0.30 g Low Dose
Reporting group description:	
TAK-018 0.30 g, tablets, orally, BID for up to 31.7 weeks.	
Reporting group title	TAK-018 1.5 g High Dose
Reporting group description:	
TAK-018 1.5 g, tablets, orally, BID for up to 26.1 weeks.	

Reporting group values	Placebo	TAK-018 0.30 g Low Dose	TAK-018 1.5 g High Dose
Number of subjects	12	11	11
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	42.97	37.42	39.25
standard deviation	± 13.133	± 16.179	± 11.297
Gender categorical Units: Subjects			
Female	5	9	3
Male	7	2	8
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	9	7	10
Unknown or Not Reported	2	3	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	7	10
More than one race	0	0	0
Unknown or Not Reported	2	4	1
Region of Enrollment Units: Subjects			
United States United States	4	3	3
Austria Austria	4	2	2
Germany Germany	1	1	4
United Kingdom	0	0	1
France France	3	5	1

Height			
Units: centimeters (cm)			
arithmetic mean	171.87	167.95	172.57
standard deviation	± 7.709	± 7.692	± 8.594
Body Mass Index (BMI)			
BMI was calculated based on the height and weight, using the formula: BMI (kg/m^2) = Weight (kg) / [Height (cm)* 0.01]^2.			
Units: kilogram per meters squared (kg/m^2)			
arithmetic mean	24.57	23.92	26.09
standard deviation	± 4.617	± 5.037	± 6.175
Weight			
Units: kilograms (kg)			
arithmetic mean	72.44	67.61	77.95
standard deviation	± 13.514	± 15.111	± 19.971

Reporting group values	Total		
Number of subjects	34		
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	17		
Male	17		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	26		
Unknown or Not Reported	6		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	27		
More than one race	0		
Unknown or Not Reported	7		
Region of Enrollment			
Units: Subjects			
United States United States	10		
Austria Austria	8		
Germany Germany	6		
United Kingdom	1		
France France	9		

Height Units: centimeters (cm) arithmetic mean standard deviation	-		
Body Mass Index (BMI)			
BMI was calculated based on the height and weight, using the formula: BMI (kg/m^2) = Weight (kg) / [Height (cm)* 0.01]^2.			
Units: kilogram per meters squared (kg/m^2) arithmetic mean standard deviation	-		
Weight Units: kilograms (kg) arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
TAK-018 placebo-matching tablets, orally, twice daily (BID) for up to 27.7 weeks.	
Reporting group title	TAK-018 0.30 g Low Dose
Reporting group description:	
TAK-018 0.30 g, tablets, orally, BID for up to 31.7 weeks.	
Reporting group title	TAK-018 1.5 g High Dose
Reporting group description:	
TAK-018 1.5 g, tablets, orally, BID for up to 26.1 weeks.	

Primary: Percentage of Participants With Endoscopic Recurrence of CD as Assessed by Rutgeerts Grading Scale at Week 26

End point title	Percentage of Participants With Endoscopic Recurrence of CD as Assessed by Rutgeerts Grading Scale at Week 26

End point description:

Endoscopic recurrence is defined as a Rutgeerts' score ≥ i2. The Rutgeerts scoring is a 5-point scale used to assess endoscopic recurrence at the ileocolonic anastomosis and preanastomotic ileum. The total score ranges from i0 to i4; where i0 = no lesions, i1= ≤ 5 aphthous ulcers, i2= > 5 aphthous ulcers with normal mucosa between lesions or lesions are confined to the anastomosis, i3= diffuse aphthous ileitis with diffusely inflamed mucosa and i4= diffuse inflammation with larger ulcers, nodules, and/or narrowing. Higher score indicates worsening. Percentages are rounded off to the nearest single decimal.

End point type	Primary
End point timeframe:	
At Week 26	

End point values	Placebo	TAK-018 0.30 g Low Dose	TAK-018 1.5 g High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	11	11	
Units: percentage of participants				
number (not applicable)	91.7	81.8	90.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-018 0.30 g Low Dose

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	Fisher exact
Parameter estimate	Estimated Difference in ERR
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.23

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v TAK-018 1.5 g High Dose
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Estimated difference in ERR
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.31

Secondary: Ctrough: Observed Plasma Trough Concentrations of TAK-018

End point title	Ctrough: Observed Plasma Trough Concentrations of TAK-018 [1]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose and at multiple time points (up to 12 hours) post-dose at Week 3

Notes:

[1] - 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: Only descriptive analysis was performed for this endpoint.

End point values	TAK-018 0.30 g Low Dose	TAK-018 1.5 g High Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: milligrams per Litre (mg/L)				
arithmetic mean (standard deviation)	13.8 (± 9.39)	36.2 (± 21.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Fecal Calprotectin (FCP) >135 Microgram per Gram (mcg/g) at Weeks 3, 6, 12, 18, 26 and 30

End point title	Percentage of Participants With Fecal Calprotectin (FCP) >135 Microgram per Gram (mcg/g) at Weeks 3, 6, 12, 18, 26 and 30

End point description:

Stool samples were collected for analysis of fecal calprotectin, a biomarker of intestinal inflammatory activity. Percentages are rounded off to the nearest single decimal.

End point type	Secondary

End point timeframe:

At Weeks 3, 6, 12, 18, 26 and 30

End point values	Placebo	TAK-018 0.30 g Low Dose	TAK-018 1.5 g High Dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	8	7	
Units: percentage of participants				
number (not applicable)				
At Week 3 (n=9, 8, 7)	55.6	75.0	42.9	
At Week 6 (n= 11, 8, 6)	27.3	50.0	83.3	
At Week 12 (n= 9, 8, 6)	44.4	37.5	33.3	
At Week 18 (n= 8, 6, 5)	75.0	50.0	60.0	
At Week 26 (n= 7, 4, 4)	71.4	75.0	50.0	
At Week 30 (n= 5, 6, 4)	40.0	66.7	25.0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 30 days following last dose of study drug (up to 35.98 weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-018 placebo-matching tablets, orally, twice daily (BID) for up to 27.7 weeks.

Reporting group title	TAK-018 1.5 g High Dose

Reporting group description:

TAK-018 1.5 g, tablets, orally, BID for up to 26.1 weeks.

Reporting group title	TAK-018 0.30 g Low Dose

Reporting group description:

TAK-018 0.30 g, tablets, orally, BID for up to 31.7 weeks.

Serious adverse events	Placebo	TAK-018 1.5 g High Dose	TAK-018 0.30 g Low Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	4 / 11 (36.36%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (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
Anastomotic leak			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood loss anaemia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
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			
Mesenteric haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (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			
Abdominal abscess			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (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

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

Non-serious adverse events	Placebo	TAK-018 1.5 g High Dose	TAK-018 0.30 g Low Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	9 / 11 (81.82%)	6 / 11 (54.55%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Anxiety			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood phosphorus decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	3 / 12 (25.00%)	1 / 11 (9.09%)	2 / 11 (18.18%)
occurrences (all)	4	1	3
Faecal calprotectin increased			
subjects affected / exposed	3 / 12 (25.00%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Haematocrit decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Platelet count increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Red blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Post procedural discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Nervous system disorders			

Tremor			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Bowel movement irregularity			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	1	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Abdominal pain			

subjects affected / exposed	2 / 12 (16.67%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	3	1	0
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Abdominal tenderness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	5 / 12 (41.67%)	2 / 11 (18.18%)	0 / 11 (0.00%)
occurrences (all)	5	2	0
Nausea			
subjects affected / exposed	3 / 12 (25.00%)	3 / 11 (27.27%)	1 / 11 (9.09%)
occurrences (all)	3	4	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	2 / 11 (18.18%)
occurrences (all)	3	0	3
Crohn's disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Sensitive skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle twitching			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Muscle tightness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sepsis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Tinea versicolour			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Escherichia urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2019	The following changes were implemented as per Amendment 1: 1. Update to include descriptive information on nonclinical findings relating to rat specific renal tubular degeneration to align with the investigator brochure (IB). 2. Update to clarify when study drug should be taken in relation to meal consumption and clarification regarding when treatment will start. 3. Update that subjects who terminate early from the study will have a final visit 30 days after their last dose of study drug. 4. Inclusion of stopping criteria for the study and for individual subjects based on Common Terminology Criteria for Adverse Events (CTCAE) grading. 5. Update to include surgeon's documentation that laparoscopic ileocecal resection removed active disease. 6. Clarification to the use of concomitant medications: those excluded postoperatively and prior to study treatment, and those permitted for subject safety and well-being. 7. Inclusion of rescreening criteria. 8. Clarification that height will be measured during screening. 9. Clarification of patient reported outcomes (PRO) reporting requirements. 10. Clarification that local laboratory results should be entered into the electronic data capture (EDC). 11. Inclusion of urinalysis assessment as part of study procedures. 12. Clarification to accurately record dosing before PK sample collections. 13. Clarification of the purpose of RNA samples. 14. Inclusion of details on compliance measurement in case of a discrepancy. 15. Replacement of AE intensity terminology with the CTCAE Version 5 scale. 16. Clarification regarding the internal monitoring committee. 17. Clarification to the statistical analyses conducted for efficacy, pharmacodynamic analysis, PRO-2, interim analysis, and determination of sample size. 18. Updates to Appendix A, Schedule of Events, to align with clarifications within the text, including PRO-2 assessment on Day 1 and EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) assessment at screening.
13 January 2020	Amendment 3 changes: 1. Addition of results from chronic toxicity studies in dogs and rats. 2. Updated information for phase 1b Study EBFIM117. 3. Changes to primary, safety, secondary, and exploratory objectives. 4. Change of primary endpoint and clarification of safety, secondary, and exploratory endpoints. 5. Updates and clarifications to overall study design based on longer duration of treatment that include addition of a stratification factor at randomization, changes to sample size, and addition of a Week 30. 6. Updated schematic of study design. 7. Addition of composition of study treatment tablets and their storage. 8. Addition of stratification of subjects by smoking status during randomization. 9. Clarifications to patient reported outcomes and to descriptions of patient-reported outcome 2 (PRO-2) and EQ 5D 5L instruments. 10. Updated time period for collection of concomitant medications and procedures. 10. Updated pregnancy testing requirements for longer treatment duration. 11. Addition of information regarding SAE reporting. 12. Corrections to statistical analyses sections. 13. Updates to Appendix A, Schedule of Events (and footnotes), to align with changes in text.
30 July 2020	The following changes were implemented as per Amendment 4: 1. Specification that the surgical procedure is a prerequisite for enrollment to the study. 2. Specification of clinic visits on Day 1 (D1) and Week 26 (W26) and that study visits at screening and on W3, W6, W12, W18, and W30 may be conducted as clinic or HHC visits. 3. Clarification regarding study drug administration related to changes in study procedures related to the pandemic. 4. Clarification regarding physical examination (PE) during HHC visits. 5. Clarification regarding where PK sample collection times are recorded. 5. Addition of information regarding changes to study procedures due to the pandemic. 6. Clarification regarding posttreatment follow-up assessments for subjects who complete the study and for those who discontinue early. 7. Correction that the safety assessment does not include electrocardiogram changes from baseline.

08 October 2021	The following changes were implemented as per Amendment 5: 1. Updates to the study signatories. 2. Addition of the International Nonproprietary Name (INN): sibofimloc.

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.

This study is terminated as the sponsor decided to discontinue study due to inability to recruit the expected number of participants within the requisite time period.

Notes: