Clinical trial results:
A phase 2, multicenter, randomized, double-blind, placebo controlled, dose-finding study to evaluate the efficacy and safety of IMU-838 for induction and maintenance therapy in moderate-to-severe ulcerative colitis (CALDOSE-1)

Summary

EudraCT number	2017-003703-22
Trial protocol	GB ES NL PL PT HR BG RO
Global end of trial date	16 November 2022

Results information

Result version number	v1 (current)
This version publication date	01 December 2023
First version publication date	01 December 2023

Trial information

Trial identification

Sponsor protocol code	P2-IMU-838-UC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03341962
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immunic AG
Sponsor organisation address	Lochhamer Schlag 21, Gräfelfing, Germany, 82166
Public contact	Chief Medical Officer, Dr Andreas Muehler , andreas.muehler@imux.com
Scientific contact	Chief Medical Officer, Dr Andreas Muehler , andreas.muehler@imux.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	16 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2022
Global end of trial reached?	Yes
Global end of trial date	16 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the optimal dose of IMU-838 to induce symptomatic remission and endoscopic healing in patients with moderate-to-severe ulcerative colitis (UC)

Protection of trial subjects:

The trial was conducted in a manner consistent with all applicable regulatory authority and independent ethics committee regulations (e.g. International Council for Harmonisation [ICH] Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95], the Declaration of Helsinki [in its currently acknowledged version] as well as in keeping with applicable local law(s) and regulation(s). Before any clinical trial-related activities were performed, the investigator (or authorized designee) reviewed the informed consent form and explained the study to the patient. The investigator ensured that the patient was fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial.
Further risk minimisation procedures included:
• specific inclusion and exclusion criteria which ensured that patients who presented with characteristics that may have increased the risk for an adverse outcome were excluded
• close monitoring for red blood cells in urine
• regular monitoring of liver enzymes
• a 1-week initiation dose at half-dose level.

Background therapy:

In induction phase the following concomitant medication was allowed:
•Oral corticosteroids: Stable dose of ≤20 mg/day prednisolone equivalent allowed, if a stable dose was given for at least 2 weeks before randomization
•Oral budesonide MMX: Stable dose of ≤9 mg/day allowed, if a stable dose was given for at least 2 weeks before randomization
•Oral beclomethasone dipropionate: Stable dose of ≤5 mg/day allowed, if same stable dose was given for at least 2 weeks before randomization
•Oral aminosalicylates (eg, mesalazines): Stable dose of ≤4 g/day allowed, if same stable dose was given for at least 3 weeks before randomization

At the start of the maintenance phase (at Weeks 10 or 22) a corticosteroid tapering regimen was to be initiated for patients receiving oral steroids. For prednisone, the dose was to be reduced at a rate of 5 mg (or equivalent) every 2 weeks. For beclomethasone dipropionate and budesonide other suitable tapering regimen were to be used according to the investigator’s discretion.

Evidence for comparator: -

Actual start date of recruitment	01 February 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	Albania: 13
Country: Number of subjects enrolled	Belarus: 6
Country: Number of subjects enrolled	Bosnia and Herzegovina: 5
Country: Number of subjects enrolled	North Macedonia: 10
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	Ukraine: 85
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czechia: 9
Worldwide total number of subjects	263
EEA total number of subjects	80

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)	242
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study had 3 phases, induction, maintenance and open-label. Patients who achieved symptomatic remission during the induction phase (IP) either at Week 10 (IP) or 22 (extended IP) could proceed to the maintenance phase (MP). Patients who were treated for at least 6 weeks could proceed into the open-label treatment extension phase (OLE).

Pre-assignment

Screening details:

Of the 598 screened patients, 263 were randomized and treated with 10, 30 or 45 mg IMU-838 or placebo.

Period 1

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

Blinding implementation details:

To maintain the blind, the IMU-838 as well as the placebo tablets had identical appearance, shape and color, and had identical labeling and packaging. To minimize the potential for bias, treatment randomization information was kept confidential by the responsible personnel and was not released to investigators, other study center personnel, or the sponsor’s designee(s) until after database hard lock for the final analysis of the induction and maintenance phase, respectively.

Arms

Are arms mutually exclusive?	No
Arm title	10 mg IMU-838

Arm description:

Two 5 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 7 days of treatment, patients received 1 tablet once daily, ie, 5 mg/day IMU-838 on Days 0 to 6. Thereafter, all patients were dosed with 2 tablets once daily, ie, 10 mg/day IMU 838 after Day 7. Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Arm title	30 mg IMU-838

Arm description:

Two 15 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 7 days of treatment, patients received 1 tablet once daily, ie, 15 mg/day IMU-838 on Days 0 to 6. Thereafter, all patients were dosed with 2 tablets once daily, ie, 30 mg/day IMU 838 after Day 7.
Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Arm title	45 mg IMU-838

Arm description:

Two 22.5 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 7 days of treatment, patients received 1 tablet once daily, ie, 22.5 mg/day IMU-838 on Days 0 to 6. Thereafter, all patients were dosed with 2 tablets once daily, ie, 45 mg/day IMU 838 after Day 7.
Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Arm title	Placebo

Arm description:

Two placebo tablets once daily.

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:

For the first 7 days of treatment, patients received 1 placebo tablet once daily on Days 0 to 6. Thereafter, all patients were dosed with 2 placebo tablets once daily.
The placebo tablets were identical to the IMU-838 tablets in terms of appearance, constitution of inactive ingredients, and packaging.

Arm title	Combined IMU-838

Arm description:

Two 15 or 22.5 mg tablets once daily of IMU-838 for 10 to 22 weeks.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 7 days of treatment, patients received 1 tablet once daily, ie, 15 mg/day or 22.5 mg/day IMU-838 on Days 0 to 6. Thereafter, all patients were dosed with 2 tablets once daily, ie, 30 mg/day or 45 mg/day IMU-838 after Day 7.
Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Number of subjects in period 1[1]	10 mg IMU-838	30 mg IMU-838	45 mg IMU-838
Started	67	66	66
Completed	53	48	50
Not completed	14	19	16
Consent withdrawn by subject	5	8	3
Physician decision	4	4	9
Other	3	5	3
Transferred to other arm/group	-	-	-
Liver enzymes	-	-	1
Lost to follow-up	2	1	-
Prohibited concomitant medication	-	1	-
Joined	0	1	0
Transferred in from other group/arm	-	1	-

Number of subjects in period 1[1]	Placebo	Combined IMU-838
Started	64	132
Completed	52	98
Not completed	12	35
Consent withdrawn by subject	5	11
Physician decision	3	13
Other	2	8
Transferred to other arm/group	1	-
Liver enzymes	-	1
Lost to follow-up	1	1
Prohibited concomitant medication	-	1
Joined	0	1
Transferred in from other group/arm	-	1

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: One patient was randomized to placebo (pbo) and erroneously received 30 mg IMU-838 instead of pbo and was included in the 30 mg IMU-838 group (and combined IMU-838 group) for the SAF but in the pbo group for the FAS. Therefore the patient was marked as transferring to another group in the pbo group and as joining from another group in the 30 mg and combined IMU-838 group.
SAF: 67 patients in the 30 mg and 63 patients in pbo group
FAS: 66 patients in the 30 mg and 64 patients in pbo group

Period 2

Period 2 title	Maintenance phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To maintain the blind, the IMU-838 as well as the placebo tablets had identical appearance, shape and color, and had identical labeling and packaging. To minimize the potential for bias, treatment randomization information was kept confidential by the responsible personnel and was not released to investigators, other study center personnel, or the sponsor's designee(s) until after database hard lock for the final analysis of the induction and maintenance phase, respectively.

Arms

Are arms mutually exclusive?	Yes
Arm title	30 mg IMU-838

Arm description:

Two 15 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were dosed with 2 tablets once daily, ie, 30 mg/day IMU 838.
The IMP was to be administered once daily as oral tablets. Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Arm title	10 mg IMU-838

Arm description:

Two 5 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were dosed with 2 tablets once daily, ie, 10 mg/day IMU 838.
The IMP was to be administered once daily as oral tablets. Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Arm title	Placebo

Arm description:

Two placebo tablets once daily.

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:

Patients were dosed with 2 placebo tablets once daily. The placebo tablets were identical to the IMU-838 tablets in terms of appearance, constitution of inactive ingredients, and packaging.

Number of subjects in period 2	30 mg IMU-838	10 mg IMU-838	Placebo
Started	40	45	27
Completed	29	35	21
Not completed	11	10	6
Physician decision	3	5	3
Consent withdrawn by subject	4	3	-
Other	3	2	3
Pregnancy	1	-	-

Period 3

Period 3 title	Open-label treatment extension (OLE)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The blinding of the individual randomized treatment assignments during the blinded treatment phase was maintained for investigators and other study personnel, as well as for patients entering the OLE arm.

Arms

Arm title	30 mg IMU-838 (OLE)

Arm description:

Two 15 mg tablets once daily of IMU-838.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were dosed with 2 tablets once daily, ie, 30 mg/day IMU 838.
The IMP was to be administered once daily as oral tablets. Tablets were to be taken once daily in the morning in fasted state with 1 glass of water approximately 15 minutes to 1 hour before breakfast. If 2 tablets needed to be taken, these were to be taken at the same time.

Number of subjects in period 3[2][3]	30 mg IMU-838 (OLE)
Started	75
Completed	0
Not completed	190
Consent withdrawn by subject	51
Physician decision	14

Study termination	115
Other	10
Joined	115
Transferred in from other group/arm	115

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients who had been treated for at least 6 weeks in the IP and fulfilled further eligibility criteria could proceed into the OLE.

115 patients transitioned directly from the IP to the OLE and received 30 mg IMU-838 and an additional 75 patients entered the OLE after the MP, resulting in a total of 190 patients in the OLE.

[3] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.

Justification: Patients who had been treated for at least 6 weeks in the IP and fulfilled further eligibility criteria could proceed into the OLE.

115 patients transitioned directly from the IP to the OLE (transferred) and received 30 mg IMU-838 and an additional 75 patients entered the OLE after the MP, resulting in a total of 190 patients in the OLE.

Baseline characteristics

Reporting groups[1]	
Reporting group title	Induction phase
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects enrolled is 263 worldwide and in the induction phase period (Baseline). The arms defined in the induction phase are not mutually exclusive.

Reporting group values	Induction phase	Total	
Number of subjects	263	263	
Age categorical 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)	242	242	
From 65-84 years	21	21	
85 years and over	0	0	
Age continuous Units: years			
median	40.0		
full range (min-max)	18 to 77	-	
Gender categorical Units: Subjects			
Female	115	115	
Male	148	148	
Current tobacco user Units: Subjects			
yes	13	13	
no	250	250	
Duration of disease			
Duration of underlying disease recorded at Baseline.			
Units: years			
arithmetic mean	6.4		
standard deviation	± 6.4	-	
Full Mayo score at Baseline			
Combined, partial (non-invasive) Mayo score (stool frequency, rectal bleeding, and physician’s global assessment) and Mayo endoscopy score			
Units: score			
arithmetic mean	9.1		
standard deviation	± 1.4	-	

Subject analysis sets	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) consisted of all randomized patients who had received at least one dose of study medication, ie, any dose of IMU-838 or placebo. The analyses based on the FAS were conducted on an intention-to-treat procedure, ie, all patients were analyzed by the groups to which they were randomized to ("intention-to-treat").
One patient was randomized to placebo but erroneously received 30 mg IMU-838 and was included in the placebo group here.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set (SAF) consisted of all randomized patients who had received at least one dose of study medication, ie, any dose of IMU-838 or placebo. If it was uncertain if the patient had received any study medication, the patient was included in the SAF. The analyses based on the SAF was conducted on an "as treated" basis, ie, all patients were analyzed by the treatment they had actually received (according to the kits dispensed, not according to the actual dose received in consideration of treatment compliance).
One patient was randomized to placebo but erroneously received 30 mg IMU-838 and was included in the 30 mg group here.

Reporting group values	Full analysis set (FAS)	Safety analysis set (SAF)	
Number of subjects	263	263	
Age categorical 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)	242	242	
From 65-84 years	21	21	
85 years and over	0	0	
Age continuous Units: years			
median	40.0	40.0	
full range (min-max)	18 to 77	18 to 77	
Gender categorical Units: Subjects			
Female	115	115	
Male	148	148	
Current tobacco user Units: Subjects			
yes	13	13	
no	250	250	
Duration of disease			
Duration of underlying disease recorded at Baseline.			
Units: years			
arithmetic mean	6.4	6.4	
standard deviation	± 6.4	± 6.4	
Full Mayo score at Baseline			

Combined, partial (non-invasive) Mayo score (stool frequency, rectal bleeding, and physician’s global assessment) and Mayo endoscopy score			
Units: score			
arithmetic mean	9.1	9.1	
standard deviation	± 1.4	± 1.4	

End points

End points reporting groups

Reporting group title	10 mg IMU-838
Reporting group description:	
Two 5 mg tablets once daily of IMU-838.	
Reporting group title	30 mg IMU-838
Reporting group description:	
Two 15 mg tablets once daily of IMU-838.	
Reporting group title	45 mg IMU-838
Reporting group description:	
Two 22.5 mg tablets once daily of IMU-838.	
Reporting group title	Placebo
Reporting group description:	
Two placebo tablets once daily.	
Reporting group title	Combined IMU-838
Reporting group description:	
Two 15 or 22.5 mg tablets once daily of IMU-838 for 10 to 22 weeks.	
Reporting group title	30 mg IMU-838
Reporting group description:	
Two 15 mg tablets once daily of IMU-838.	
Reporting group title	10 mg IMU-838
Reporting group description:	
Two 5 mg tablets once daily of IMU-838.	
Reporting group title	Placebo
Reporting group description:	
Two placebo tablets once daily.	
Reporting group title	30 mg IMU-838 (OLE)
Reporting group description:	
Two 15 mg tablets once daily of IMU-838.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) consisted of all randomized patients who had received at least one dose of study medication, ie, any dose of IMU-838 or placebo. The analyses based on the FAS were conducted on an intention-to-treat procedure, ie, all patients were analyzed by the groups to which they were randomized to (“intention-to-treat”). One patient was randomized to placebo but erroneously received 30 mg IMU-838 and was included in the placebo group here.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set (SAF) consisted of all randomized patients who had received at least one dose of study medication, ie, any dose of IMU-838 or placebo. If it was uncertain if the patient had received any study medication, the patient was included in the SAF. The analyses based on the SAF was conducted on an “as treated” basis, ie, all patients were analyzed by the treatment they had actually received (according to the kits dispensed, not according to the actual dose received in consideration of treatment compliance). One patient was randomized to placebo but erroneously received 30 mg IMU-838 and was included in the 30 mg group here.	

Primary: Symptomatic remission and endoscopic healing at Week 10

End point title	Symptomatic remission and endoscopic healing at Week 10[1]

End point description:

Composite end point: Proportion of patients with both, symptomatic remission (Mayo rectal bleeding subscore = 0 and Mayo stool frequency subscore of 0 or 1) and endoscopic healing (Modified Mayo endoscopy subscore of 0 or 1) at Week 10. All patients who were randomized to 30 mg/day and 45 mg/day were used for the assessment of the primary efficacy end point.

End point type	Primary

End point timeframe:

10 weeks

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: The pre-specified primary end point included only the comparison between the combined 30 and 45 mg IMU-838 groups and placebo.

End point values	Placebo	Combined IMU-838		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[2]	116[3]		
Units: patient				
yes	8	16		
no	49	100		

Notes:

[2] - FAS, N=7 missing

[3] - FAS, N=16 missing

Statistical analyses

Statistical analysis title	Difference in proportion of patients

Statistical analysis description:

Difference in proportion of patients achieving end point

Comparison groups	Placebo v Combined IMU-838
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5836 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.13
upper limit	15.28

Notes:

[4] - 1-sided exact Cochran-Mantel-Haenszel test adjusted for stratification factors (prior use of any biologics and concurrent use of corticosteroids), α=0.097.

Secondary: Induction phase: Time to achieving symptomatic remission

End point title	Induction phase: Time to achieving symptomatic remission[5]

End point description:

Time to achieving symptomatic remission (Mayo rectal bleeding subscore = 0 and Mayo stool frequency subscore of 0 or 1)

End point type	Secondary

End point timeframe:

22 weeks

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: The pre-specified end point included only the comparison between the combined 30 and 45 mg IMU-838 groups and placebo.

End point values	Placebo	Combined IMU-838		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[6]	132[7]		
Units: days				
arithmetic mean (standard error)	119.6 (± 7.1)	108.8 (± 5.5)		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Induction Phase: Proportion of patients with clinical response at Week 10

End point title	Induction Phase: Proportion of patients with clinical response at Week 10[8]

End point description:

Proportion of patients with clinical response (decrease from Baseline in the full Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1) at Week 10

End point type	Secondary

End point timeframe:

10 weeks

Notes:

[8] - 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: The pre-specified end point included only the comparison between the combined 30 and 45 mg IMU-838 groups and placebo.

End point values	Placebo	Combined IMU-838		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[9]	114[10]		
Units: Number of patients				
yes	27	50		
no	30	64		

Notes:

[9] - FAS, N=7 missing

[10] - FAS, N=18 missing

Statistical analyses

No statistical analyses for this end point

Secondary: Induction Phase: Proportion of patients with endoscopic healing at Week 10

End point title	Induction Phase: Proportion of patients with endoscopic healing at Week 10[11]

End point description:

Proportion of patients with endoscopic healing (Modified Mayo endoscopy subscore of 0 or 1) at Week 10

End point type	Secondary

End point timeframe:

10 weeks

Notes:

[11] - 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: The pre-specified end point included only the comparison between the combined 30 and 45 mg IMU-838 groups and placebo.

End point values	Placebo	Combined IMU-838		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[12]	112[13]		
Units: number of patients				
yes	12	28		
no	45	84		

Notes:

[12] - FAS, N=7 missing

[13] - FAS, N=20 missing

Statistical analyses

No statistical analyses for this end point

Secondary: Induction Phase: Proportion of patients with symptomatic response

End point title	Induction Phase: Proportion of patients with symptomatic response[14]

End point description:

Proportion of patients with symptomatic response (≥1-point decrease from Baseline in Mayo PRO-2 score [Mayo patient-reported outcome score, ie, stool frequency and rectal bleeding score on a 4-point scale]) during the extended IP

End point type	Secondary

End point timeframe:

22 weeks

Notes:

[14] - 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: The pre-specified end point included only the comparison between the combined 30 and 45 mg IMU-838 groups and placebo.

End point values	Placebo	Combined IMU-838		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[15]	128[16]		
Units: number of patients				
yes	49	101		
no	13	27		

Notes:

[15] - FAS, N=2 missing

[16] - FAS, N=4 missing

Statistical analyses

No statistical analyses for this end point

Secondary: Induction Phase: Full Mayo score

End point title	Induction Phase: Full Mayo score

End point description:

Change in full Mayo score from Baseline to Week 10. The full Mayo score is composed of 4 categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) each rated from 0 to 3 that are added up to give a total score that ranges from 0 to 12. A higher score indicates a worse outcome.

End point type	Secondary

End point timeframe:

10 weeks

End point values	10 mg IMU-838	30 mg IMU-838	45 mg IMU-838	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67[17]	65[18]	66[19]	64[20]
Units: Mayo score				
arithmetic mean (standard deviation)				
Baseline Day 0	9.0 (± 1.6)	9.1 (± 1.4)	9.1 (± 1.4)	9.1 (± 1.4)
Change from Baseline at Week 10	-3.0 (± 2.6)	-2.5 (± 2.7)	-2.8 (± 2.7)	-2.3 (± 2.7)

Notes:

[17] - N= 61 at Week 10

[18] - N=53 at Week 10

[19] - N=59 at Week 10

[20] - N=57 at Week 10

End point values	Combined IMU-838			
Subject group type	Reporting group			
Number of subjects analysed	131[21]			
Units: Mayo score				
arithmetic mean (standard deviation)				
Baseline Day 0	9.1 (± 1.4)			
Change from Baseline at Week 10	-2.6 (± 2.7)			

Notes:

[21] - N=112 at Week 10

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Proportion of patients in symptomatic remission

End point title	Maintenance Phase: Proportion of patients in symptomatic remission

End point description:

Proportion of patients in symptomatic remission (Mayo rectal bleeding subscore = 0 and Mayo stool frequency subscore of 0 or 1) by visit up to Week 50

End point type	Secondary

End point timeframe:

50 weeks

End point values	30 mg IMU-838	10 mg IMU-838	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40[22]	45[23]	27[24]	
Units: number of patients				
Week 14	14	16	7	
Week 30	23	33	19	
Week 50	24	27	16	

Notes:

[22] - N=20 at Week 14
N=33 at Week 30
N=29 at Week 50
[23] - N=19 at Week 14
N=40 at Week 30
N=33 at Week 50
[24] - N=11 at Week 14
N=24 at Week 30
N=21 at Week 50

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance Phase: Corticosteroid-free clinical remission

End point title	Maintenance Phase: Corticosteroid-free clinical remission

End point description:

The proportion of patients with clinical remission at Week 50 and no receipt of systemic or local corticosteroids during 8 weeks before Week 50.

End point type	Secondary

End point timeframe:

50 weeks

End point values	30 mg IMU-838	10 mg IMU-838	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	18	
Units: number of patients	16	10	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 4 years including induction phase (IP, up to 22 weeks), maintenance phase (MP, up to 40 weeks) and open-label treatment extension (OLE).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	10 mg IMU-838 (IP)
Reporting group description: Two 5 mg tablets once daily of IMU-838.	
Reporting group title	30 mg IMU-838 (IP)
Reporting group description: Two 15 mg tablets once daily of IMU-838.	
Reporting group title	45 mg IMU-838 (IP)
Reporting group description: Two 22.5 mg tablets once daily of IMU-838.	
Reporting group title	Placebo (IP)
Reporting group description: Two placebo tablets once daily.	
Reporting group title	10 mg IMU-838 (MP)
Reporting group description: Two 5 mg tablets once daily of IMU-838.	
Reporting group title	30 mg IMU-838 (MP)
Reporting group description: Two 15 mg tablets once daily of IMU-838.	
Reporting group title	Placebo (MP)
Reporting group description: Two placebo tablets once daily.	
Reporting group title	30 mg IMU-838 (OLE)
Reporting group description: Two 15 mg tablets once daily of IMU-838.	

Serious adverse events	10 mg IMU-838 (IP)	30 mg IMU-838 (IP)	45 mg IMU-838 (IP)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 67 (2.99%)	5 / 67 (7.46%)	5 / 66 (7.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			

subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 66 (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
Hepatic enzyme increased			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	0 / 66 (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
Lower limb fracture			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Road traffic accident			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Skull fracture			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Spinal compression fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	0 / 66 (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

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 67 (1.49%)	1 / 67 (1.49%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 66 (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
Haematochezia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Inguinal hernia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Large intestine perforation			

subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Volvulus			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 66 (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			
Cholecystitis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	0 / 66 (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
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Renal colic			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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			
Abscess limb			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
COVID-19 pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Colon gangrene			

subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Sepsis			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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
Urinary tract infection			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	0 / 66 (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

Serious adverse events	Placebo (IP)	10 mg IMU-838 (MP)	30 mg IMU-838 (MP)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	3 / 45 (6.67%)	2 / 40 (5.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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

Hepatic enzyme increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Lower limb fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Road traffic accident			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Skull fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Spinal compression fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 63 (0.00%)	1 / 45 (2.22%)	0 / 40 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	1 / 40 (2.50%)
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			
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Haematochezia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Inguinal hernia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Large intestine perforation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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

Umbilical hernia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Volvulus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Proctitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 45 (2.22%)	0 / 40 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Renal colic			

subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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			
Abscess limb			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
COVID-19 pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 45 (2.22%)	0 / 40 (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
Colon gangrene			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Peritonitis			

subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Sepsis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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
Urinary tract infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 45 (0.00%)	0 / 40 (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

Serious adverse events	Placebo (MP)	30 mg IMU-838 (OLE)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	14 / 190 (7.37%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 27 (0.00%)	3 / 190 (1.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Volvulus			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			

subjects affected / exposed	1 / 27 (3.70%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon gangrene			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			

subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	10 mg IMU-838 (IP)	30 mg IMU-838 (IP)	45 mg IMU-838 (IP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 67 (11.94%)	7 / 67 (10.45%)	12 / 66 (18.18%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 67 (4.48%)	1 / 67 (1.49%)	1 / 66 (1.52%)
occurrences (all)	3	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 67 (2.99%)	5 / 67 (7.46%)	3 / 66 (4.55%)
occurrences (all)	2	5	3
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 67 (1.49%)	0 / 67 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	5 / 66 (7.58%)
occurrences (all)	0	0	7
Infections and infestations			
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 67 (2.99%)	1 / 67 (1.49%)	2 / 66 (3.03%)
occurrences (all)	2	1	2
Urinary tract infection			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	1 / 66 (1.52%)
occurrences (all)	0	1	1

Non-serious adverse events	Placebo (IP)	10 mg IMU-838 (MP)	30 mg IMU-838 (MP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 63 (20.63%)	7 / 45 (15.56%)	6 / 40 (15.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 63 (6.35%)	0 / 45 (0.00%)	1 / 40 (2.50%)
occurrences (all)	4	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 63 (4.76%)	1 / 45 (2.22%)	1 / 40 (2.50%)
occurrences (all)	3	1	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 63 (4.76%)	0 / 45 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 63 (1.59%)	0 / 45 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Infections and infestations			
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	2 / 63 (3.17%)	5 / 45 (11.11%)	1 / 40 (2.50%)
occurrences (all)	2	5	1
Urinary tract infection			

subjects affected / exposed	1 / 63 (1.59%)	1 / 45 (2.22%)	2 / 40 (5.00%)
occurrences (all)	1	1	2

Non-serious adverse events	Placebo (MP)	30 mg IMU-838 (OLE)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)	24 / 190 (12.63%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 27 (0.00%)	5 / 190 (2.63%)	
occurrences (all)	0	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 27 (7.41%)	5 / 190 (2.63%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 27 (0.00%)	2 / 190 (1.05%)	
occurrences (all)	0	2	
Infections and infestations			
COVID-19			
alternative dictionary used: MedDRA 23.1			
subjects affected / exposed	0 / 27 (0.00%)	14 / 190 (7.37%)	
occurrences (all)	0	14	
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	3 / 190 (1.58%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2017	The following major changes were included in Version 2.0 compared with Version 1.0: o IP-10 (IFNγ induced protein) was deleted from the list of cytokines which were to be assessed.
21 November 2017	The following major changes were included in Version 3.0 compared with Version 2.0: o Label specification was modified o Storage conditions were modified due to new stability data
17 September 2019	The following major changes were included in Version 4.0 compared with Version 3.0: o The results of the interim analysis led to the conclusion that all 3 IMU-838 doses would be continued in Enrollment Period 2. o Additional countries in which the trial was to be performed were added ie, Albania, Belarus, Bosnia-Herzegovina, North Macedonia, Norway, and Turkey. o Additional requirement for active disease in Inclusion Criterion 4 (Mayo rectal bleeding score of >=1) was added. o It was specified that care should be exercised when using medications that are substrates of the breast cancer resistance protein transport system (other prohibited and restricted medication). o Time of interim analysis adjusted to what was to be specified in the statistical analysis plan (SAP) for the interim analysis, ie, that the interim analysis will be conducted when in Enrollment Period 1 approximately 60 patients have been randomized and had received at least 1 dose of investigational medicinal product instead of 'after approximately 60 patients had completed their Week 10/end of induction assessments'. o For Screening Visit 1 (SCV1) the following footnote was added in the schedule of assessments: 'Within 30 days of Day 0. If there is a delay in assessments from SCV1 or assessments need to be repeated due to technical difficulties, assessments from SCV1 are valid for up to 60 days between SCV1 and randomization. If 60 days are exceeded, SCV1-assessments must be repeated'. o It was decided not to disclose any group level data of the interim analysis after Enrollment Period 1 or of the exploratory analysis of the MP to the Steering Committee. o In addition, as group level data were no longer disclosed it was considered appropriate not to finalize all SAPs before the interim analysis. The SAP for the induction phase that describes the primary end point analysis, however, was finalized before the interim analysis as scheduled. o overdosing not AE but protocol deviation
26 February 2021	The following major changes were included in Version 5.0 compared with Version 4.0: o It was clarified that the pharmacodynamics period that is scheduled at the start of the OLE period could be performed not only after completion of the MP but also after the IP or extended IP. o It was clarified that any human immunodeficiency virus (HIV) , hepatitis B or C virus antigen or antibody screening test that shows reactive or borderline results (not as previously only a positive HIV-Ag/Ab test) were to be confirmed via Nucleic Acid Amplification Test (Exclusion criterion 9).

14 December 2021	The following major changes were included in Version 6.0 compared with Version 5.0: o It was added that patients in the OLE may be transferred to a separate long-term follow-up study or to commercial IMU-838 (if applicable and patients have access). o Uric acid was deleted from the urinalysis assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported