Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Ulcerative Colitis

Summary

EudraCT number	2016-000642-62
Trial protocol	NL LV PT FI DE GR SE GB AT CZ LT IE BE HU ES SK PL FR HR NO IT RO
Global end of trial date	14 January 2021

Results information

Result version number	v1
This version publication date	23 July 2021
First version publication date	23 July 2021

Trial information

Trial identification

Sponsor protocol code	M14-675

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03653026
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Services, AbbVie, 001 00-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbViw, 001 00-633-9110, abbvieclinicaltrials@abbvie.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy and safety of upadacitinib 45 mg once daily (QD) compared to placebo in inducing clinical remission (per the Adapted Mayo score) in subjects with moderately to severely active ulcerative colitis (UC) who have demonstrated inadequate response, loss of response, or intolerance to oral aminosalicylates, immunosuppressants, corticosteroids, and/or biologic therapies.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 December 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	Argentina: 7
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 34

Country: Number of subjects enrolled	Japan: 81
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Norway: 22
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 117
Worldwide total number of subjects	522
EEA total number of subjects	151

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)	9
Adults (18-64 years)	466
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a Screening Period of up to 5 weeks, Part 1, and Part 2. Part 1 was a randomized, double-blind, placebo-controlled 8-week induction period. Part 2 was an open-label, 8 week extended treatment period for clinical non-responders from Part 1. A total of 522 subjects were randomized at 204 sites in 41 countries.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to upadacitinib or placebo. Randomization was stratified by bio-IR status, corticosteroid use, and Adapted Mayo score at Baseline. Within bio-IR, randomization was further stratified by number of prior biologic treatments. Within non-bio-IR, randomization was further stratified by previous biologic use.

Period 1

Period 1 title	Part 1: Placebo-controlled Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Upadacitinib 45 mg

Arm description:

Participants received 45 mg upadacitinib once daily (QD) for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Upadacitinib 45 mg administered orally once daily.

Arm title	Placebo

Arm description:

Participants received placebo matching to upadacitinib once daily for 8 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:

Administered orally once daily.

Number of subjects in period 1	Upadacitinib 45 mg	Placebo
Started	345	177
Received Treatment	344	177
Completed	334	164
Not completed	11	13
Consent withdrawn by subject	6	4
Adverse event, non-fatal	5	6
Other	-	3

Period 2

Period 2 title	Part 2: Open-label Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Upadacitinib 45 mg / Upadacitinib 45 mg

Arm description:

Participants initially assigned to upadacitinib who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 additional weeks in the open-label extension period.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Upadacitinib 45 mg administered orally once daily.

Arm title	Placebo / Upadacitinib 45 mg

Arm description:

Participants initially assigned to placebo who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 weeks in the open-label extension period.

Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Upadacitinib 45 mg administered orally once daily.

Number of subjects in period 2[1]	Upadacitinib 45 mg / Upadacitinib 45 mg	Placebo / Upadacitinib 45 mg
Started	68	116
Completed	65	111
Not completed	3	5
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	1
Other	1	2

Notes:

[1] - 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: Part 2 was an open label, 8-week extended treatment period for subjects who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1.

Baseline characteristics

Reporting groups	
Reporting group title	Upadacitinib 45 mg
Reporting group description:	
Participants received 45 mg upadacitinib once daily (QD) for 8 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching to upadacitinib once daily for 8 weeks.	

Reporting group values	Upadacitinib 45 mg	Placebo	Total
Number of subjects	345	177	522
Age categorical Units: Subjects			
< 18 years	6	3	9
≥ 18 years - < 40 years	160	81	241
≥ 40 years - < 65 years	146	79	225
≥ 65 years	33	14	47
Age continuous Units: years			
arithmetic mean	42.2	42.2	
standard deviation	± 14.73	± 14.44	-
Gender categorical Units: Subjects			
Female	129	67	196
Male	216	110	326
Race Units: Subjects			
White	238	127	365
Black or African American	11	6	17
Asian	94	41	135
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
Multiple	2	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	26	16	42
Not Hispanic or Latino	319	161	480
Biologic-inadequate Responder (Bio-IR) Status			
Biologic-inadequate responders (Bio-IR) are defined as subjects who had inadequate response, loss of response, or intolerance to biologic therapy. Non-biologic-inadequate responders (non-bio-IR) are defined as subjects who had inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy.			
Units: Subjects			
Bio-IR	175	91	266
Non-Bio-IR	170	86	256
Baseline Corticosteroid Use Units: Subjects			

Yes	123	75	198
No	222	102	324
Adapted Mayo Score			
The Adapted Mayo Score is a composite score of UC disease activity based on the following 3 subscores: 1) Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal). 2) Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed). 3) Endoscopic subscore, scored from 0 (normal or inactive disease) to 3 (severe disease, spontaneous bleeding, ulceration). The overall Adapted Mayo Score ranges from 0 to 9 where higher scores represent more severe disease.			
Units: Subjects			
≤ 7	205	104	309
> 7	138	73	211
Missing	2	0	2
Bio-IR Subjects: Number of Prior Biologic Treatments Units: Subjects			
≤ 1	58	33	91
> 1	117	58	175
NA (Non-bio-IR)	170	86	256
Non-Bio-IR Subjects: Prior Exposure to Biologic Therapy Units: Subjects			
Yes	1	5	6
No	169	81	250
NA (Bio-IR)	175	91	266
Disease Duration			
Data are available for 344 and 177 participants in each arm, respectively.			
Units: years			
arithmetic mean	7.273	7.584	
standard deviation	± 6.4459	± 7.6701	-
Adapted Mayo Score			
The Adapted Mayo Score is a composite score of UC disease activity based on the following 3 subscores: 1) Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal). 2) Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed). 3) Endoscopic subscore, scored from 0 (normal or inactive disease) to 3 (severe disease, spontaneous bleeding, ulceration). The overall score ranges from 0 to 9 where higher scores represent more severe disease. Data were available for 343 ad 177 subjects in each arm, respectively.			
Units: units on a scale			
arithmetic mean	7.00	7.05	
standard deviation	± 1.216	± 1.236	-

End points

End points reporting groups

Reporting group title	Upadacitinib 45 mg
Reporting group description:	
Participants received 45 mg upadacitinib once daily (QD) for 8 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching to upadacitinib once daily for 8 weeks.	
Reporting group title	Upadacitinib 45 mg / Upadacitinib 45 mg
Reporting group description:	
Participants initially assigned to upadacitinib who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 additional weeks in the open-label extension period.	
Reporting group title	Placebo / Upadacitinib 45 mg
Reporting group description:	
Participants initially assigned to placebo who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 weeks in the open-label extension period.	

Primary: Percentage of Participants who Achieved Clinical Remission per Adapted Mayo Score at Week 8

End point title	Percentage of Participants who Achieved Clinical Remission per Adapted Mayo Score at Week 8
End point description:	
The Adapted Mayo Score is a composite score of UC disease activity based on the following 3 subscores: 1) Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal). 2) Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed). 3) Endoscopic subscore, scored from 0 (normal or inactive disease) to 3 (severe disease, spontaneous bleeding, ulceration). The overall Adapted Mayo score ranges from 0 to 9 where higher scores represent more severe disease. Clinical Remission is defined as an Adapted Mayo score ≤ 2, with SFS ≤ 1 and not higher than Baseline, RBS of 0, and endoscopic subscore ≤ 1. The Part 1 intent-to-treat population (ITT1) includes randomized subjects who received at least 1 dose of study drug in Part 1. The ITT1 population excludes 6 subjects from 1 site with non-compliance. Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.	
End point type	Primary
End point timeframe:	
Week 8	

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[1]	174[2]		
Units: percentage of participants				
number (confidence interval 95%)	33.5 (28.5 to 38.5)	4.1 (1.1 to 7.1)		

Notes:

[1] - ITT1 population

[2] - ITT1 population

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	29
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.2
upper limit	34.7

Notes:

[3] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[4] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants with Endoscopic Improvement at Week 8

End point title	Percentage of Participants with Endoscopic Improvement at Week 8

End point description:

Endoscopic improvement is defined as an endoscopic subscore of 0 or 1. Endoscopies were assessed by a blinded central reader and scored according to the following scale: 0 = Normal or inactive disease; 1 = Mild disease (erythema, decreased vascular pattern); 2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration).
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[5]	174[6]		
Units: percentage of participants				
number (confidence interval 95%)	44.0 (38.8 to 49.3)	8.3 (4.1 to 12.5)		

Notes:
[5] - ITT1 population
[6] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Endoscopic Improvement
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	35.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.6
upper limit	41.6

Notes:
[7] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).
[8] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants with Endoscopic Remission at Week 8

End point title	Percentage of Participants with Endoscopic Remission at Week 8

End point description:

Endoscopic remission is defined as an endoscopic subscore of 0. Endoscopies were assessed by a blinded central reader and scored according to the following scale: 0 = Normal or inactive disease; 1 = Mild disease (erythema, decreased vascular pattern); 2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration).
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[9]	174[10]		
Units: percentage of participants				
number (confidence interval 95%)	18.2 (14.1 to 22.3)	1.7 (0.0 to 3.7)		

Notes:

[9] - ITT1 population

[10] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Endoscopic Remission
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.4
upper limit	20.3

Notes:

[11] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[12] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants Achieving Clinical Response per Adapted Mayo Score at Week 8

End point title	Percentage of Participants Achieving Clinical Response per Adapted Mayo Score at Week 8

End point description:

The Adapted Mayo Score is a composite score of UC disease activity based on the following 3 subscores:
1) Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal).
2) Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed).
3) Endoscopic subscore, scored from 0 (normal or inactive disease) to 3 (severe disease with spontaneous bleeding, ulceration).
The overall Adapted Mayo score ranges from 0 to 9 with higher scores representing more severe disease.
Clinical response per the Adapted Mayo Score is defined as a decrease in Adapted Mayo score ≥ 2 points and ≥ 30% from Baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[13]	174[14]		
Units: percentage of participants				
number (confidence interval 95%)	74.5 (69.9 to 79.1)	25.4 (18.9 to 31.8)		

Notes:

[13] - ITT1 population

[14] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Clinical Response
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	49.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.7
upper limit	57.1

Notes:

[15] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).
[16] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants Achieving Clinical Response per Partial Adapted Mayo Score at Week 2

End point title	Percentage of Participants Achieving Clinical Response per Partial Adapted Mayo Score at Week 2

End point description:

The Partial Adapted Mayo Score is a composite score of UC disease activity based on the following 2 subscores:
1) Stool frequency subscore (SFS), scored from 0 (normal number of stools) to 3 (5 or more stools more than normal).
2) Rectal bleeding subscore (RBS), scored from 0 (no blood seen) to 3 (blood alone passed).
The overall Partial Adapted Mayo score ranges from 0 to 6 with higher scores representing more severe disease.
Clinical response per Partial Adapted Mayo Score is defined as a decrease in Partial Adapted Mayo score ≥ 1 point and ≥ 30% from Baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 2

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[17]	174[18]		
Units: percentage of participants				
number (confidence interval 95%)	63.3 (58.2 to 68.5)	25.9 (19.4 to 32.4)		

Notes:

[17] - ITT1 population

[18] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Clinical Response at Week 2
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	37
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.8
upper limit	45.1

Notes:

[19] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[20] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants Who Achieved Histologic-Endoscopic Mucosal Improvement at Week 8

End point title	Percentage of Participants Who Achieved Histologic-Endoscopic Mucosal Improvement at Week 8

End point description:

Histologic endoscopic mucosal improvement is defined as an endoscopic subscore of 0 or 1 and a Geboes score ≤ 3.1.
The endoscopic subscore ranges from 0 (normal or inactive disease) to 3 (severe disease with spontaneous bleeding, ulceration).
The Geboes histologic index includes seven histological features (architectural change, chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction and erosion or ulcers). The Geboes score has 6 grades, each with 3-5 subgrades: Grade 0, structural change only; Grade 1, chronic inflammation; Grade 2, lamina propria neutrophils and eosinophils; Grade 3, neutrophils in epithelium; Grade 4, crypt destruction; and Grade 5, erosions or ulceration.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[21]	174[22]		
Units: percentage of participants				
number (confidence interval 95%)	36.7 (31.6 to 41.8)	5.8 (2.3 to 9.4)		

Notes:

[21] - ITT1 population

[22] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Histologic-Endoscopic Improvement
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.1
upper limit	36.2

Notes:

[23] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[24] - Cochran-Mantel-Haenszel test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants who Reported No Bowel Urgency at Week 8

End point title	Percentage of Participants who Reported No Bowel Urgency at Week 8

End point description:

Bowel urgency was assessed by participants in a subject diary completed once a day.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[25]	174[26]		
Units: percentage of participants				
number (confidence interval 95%)	53.7 (48.4 to 59.0)	25.9 (19.4 to 32.4)		

Notes:

[25] - ITT1 population

[26] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Bowel Urgency
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	19
upper limit	35.3

Notes:

[27] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[28] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (<= 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants who Reported No Abdominal Pain at Week 8

End point title	Percentage of Participants who Reported No Abdominal Pain at Week 8

End point description:

Abdominal pain was assessed by participants in a subject diary completed once a day. The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[29]	174[30]		
Units: percentage of participants				
number (confidence interval 95%)	53.7 (48.4 to 59.0)	24.1 (17.8 to 30.5)		

Notes:
[29] - ITT1 population
[30] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Abdominal Pain
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.001 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.9
upper limit	37.4

Notes:
[31] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).
[32] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Percentage of Participants Who Achieved Histologic Improvement at Week 8

End point title	Percentage of Participants Who Achieved Histologic Improvement at Week 8

End point description:

Histologic improvement is defined as a decrease from Baseline in Geboes score.
The Geboes histologic index includes seven histological features (architectural change, chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction and erosion or ulcers). The Geboes score has 6 grades, each with 3-5 subgrades: Grade 0, structural change only; Grade 1, chronic inflammation; Grade 2, lamina propria neutrophils and eosinophils; Grade 3, neutrophils in epithelium; Grade 4, crypt destruction; and Grade 5, erosions or ulceration.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[33]	174[34]		
Units: percentage of participants				
number (confidence interval 95%)	62.2 (57.0 to 67.3)	24.5 (18.0 to 30.9)		

Notes:

[33] - ITT1 population

[34] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Histologic Improvement
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.001 [36]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	37.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.8
upper limit	46.1

Notes:

[35] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[36] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 8

End point title	Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 8

End point description:

The Inflammatory Bowel Disease Questionnaire (IBDQ) is used to assess health-related quality of life (HRQoL) in patients with ulcerative colitis. It consists of 32 questions evaluating bowel and systemic symptoms, as well as emotional and social functions. Each question is answered on a scale from 1 (worst) to 7 (best). The total score ranges from 32 to 224 with higher scores indicating better health-related quality of life. A positive change from Baseline indicates improvement.
The analysis was conducted in the ITT1 population with available data; a mixed effect model repeat measurement (MMRM) analysis with data from observed cases up to Week 8 was used except for measurements at or after the occurrence of UC-related corticosteroids intercurrent event were excluded.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[37]	156[38]		
Units: units on a scale				
least squares mean (confidence interval 95%)	52.2 (48.57 to 55.92)	21.1 (15.98 to 26.17)		

Notes:

[37] - ITT1 population with available data

[38] - ITT1 population with available data

Statistical analyses

Statistical analysis title	Analysis of Change in IBDQ Total Score
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.001 [40]
Method	Mixed-effect model repeated measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	31.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.98
upper limit	37.36
Variability estimate	Standard error of the mean
Dispersion value	3.15

Notes:

[39] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[40] - Mixed-Effect Model Repeat Measurement with Baseline, treatment, visit, treatment by visit interaction, and strata (Baseline corticosteroid use, Baseline Adapted Mayo score, bio-IR status) in the model.

Secondary: Percentage of Participants Who Achieved Mucosal Healing at Week 8

End point title	Percentage of Participants Who Achieved Mucosal Healing at Week 8

End point description:

Mucosal healing is defined as an endoscopic score of 0 and Geboes score < 2.0.
The endoscopic subscore ranges from 0 (normal or inactive disease) to 3 (severe disease with spontaneous bleeding, ulceration).
The Geboes histologic index includes seven histological features (architectural change, chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction and erosion or ulcers). The Geboes score has 6 grades, each with 3-5 subgrades: Grade 0, structural change only; Grade 1, chronic inflammation; Grade 2, lamina propria neutrophils and eosinophils; Grade 3, neutrophils in epithelium; Grade 4, crypt destruction; and Grade 5, erosions or ulceration.
The analysis was conducted in the ITT1 population; non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 was used.

End point type	Secondary

End point timeframe:

Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341[41]	174[42]		
Units: percentage of participants				
number (confidence interval 95%)	13.5 (9.9 to 17.1)	1.7 (0.0 to 3.7)		

Notes:

[41] - ITT1 population

[42] - ITT1 population

Statistical analyses

Statistical analysis title	Analysis of Mucosal Healing
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	< 0.001 [44]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.2
upper limit	15.3

Notes:

[43] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[44] - Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) for the comparison of two treatment groups.

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score at Week 8

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score at Week 8

End point description:

The FACIT fatigue questionnaire was developed to assess fatigue associated with anemia. It consists of 13 fatigue-related questions. Each question is answered on a 5-point Likert scale: 0 (not at all); 1 (a little bit); 2 (somewhat); 3 (quite a bit); and 4 (very much). The total score ranges from 0 to 52, where higher scores represent less fatigue, and a positive change from Baseline indicates improvement.
The analysis was conducted in the ITT1 population with available data; a mixed effect model repeat measurement (MMRM) analysis with data from observed cases up to Week 8 was used except for measurements at or after the occurrence of UC-related corticosteroids intercurrent event were excluded.

End point type	Secondary

End point timeframe:

Baseline and Week 8

End point values	Upadacitinib 45 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	312[45]	155[46]		
Units: units on a scale				
least squares mean (confidence interval 95%)	9.4 (8.38 to 10.48)	3.5 (2.02 to 4.92)		

Notes:

[45] - ITT1 population with available data

[46] - ITT1 population with available data

Statistical analyses

Statistical analysis title	Analysis of Change in FACIT-F
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	< 0.001 [48]
Method	Mixed-effect model repeated measurement
Parameter estimate	LS Mean Difference
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.19
upper limit	7.73
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[47] - The primary and ranked secondary efficacy endpoints were tested with multiplicity adjustment using a fixed-sequence multiple testing procedure to ensure a strong control of family-wise type I error rate at significance level alpha = 0.05 (2-sided).

[48] - Mixed-Effect Model Repeat Measurement with Baseline, treatment, visit, treatment by visit interaction, and strata (Baseline corticosteroid use, Baseline Adapted Mayo score, bio-IR status) in the model.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: From first dose of study drug up to 30 days after the last dose or until first dose of study drug in Part 2 or first dose of study drug in M14-234 (maintenance study) or M14-533 (long term extension).

Adverse event reporting additional description:

Time Frame for Part 2: From the first dose of study drug in Part 2 up to 30 days after last dose or until first dose of study drug in M14-234 (maintenance study) or the first dose date of study drug in M14-533 (long-term extension study).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Part 1: Upadacitinib 45 mg

Reporting group description:

Participants received 45 mg upadacitinib once daily (QD) for 8 weeks.

Reporting group title	Part 1: Placebo

Reporting group description:

Participants received placebo matching to upadacitinib once daily for 8 weeks.

Reporting group title	Part 2: Upadacitinib 45 mg / Upadacitinib 45 mg

Reporting group description:

Participants initially assigned to upadacitinib who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 additional weeks in the open-label extension period.

Reporting group title	Part 2: Placebo / Upadacitinib 45 mg

Reporting group description:

Participants initially assigned to placebo who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 received upadacitinib 45 mg once daily for 8 weeks in the open-label extension period.

Serious adverse events	Part 1: Upadacitinib 45 mg	Part 1: Placebo	Part 2: Upadacitinib 45 mg / Upadacitinib 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 344 (3.20%)	8 / 177 (4.52%)	1 / 68 (1.47%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
GASTROINTESTINAL STOMA NECROSIS			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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
HAND FRACTURE			

subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (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
Vascular disorders			
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 344 (0.29%)	1 / 177 (0.56%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (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
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 344 (0.00%)	0 / 177 (0.00%)	0 / 68 (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
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 344 (0.00%)	0 / 177 (0.00%)	0 / 68 (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
COLITIS			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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
COLITIS ULCERATIVE			

subjects affected / exposed	4 / 344 (1.16%)	3 / 177 (1.69%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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 / 344 (0.00%)	0 / 177 (0.00%)	0 / 68 (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 EMBOLISM			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
PYODERMA GANGRENOSUM			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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
Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 PNEUMONIA			
subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (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
DENGUE FEVER			

subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (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
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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
ESCHERICHIA INFECTION			
subjects affected / exposed	0 / 344 (0.00%)	1 / 177 (0.56%)	0 / 68 (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
Metabolism and nutrition disorders			
MALNUTRITION			
subjects affected / exposed	1 / 344 (0.29%)	0 / 177 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Placebo / Upadacitinib 45 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 116 (3.45%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
GASTROINTESTINAL STOMA NECROSIS			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HAND FRACTURE			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
PELVIC VENOUS THROMBOSIS			

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ABDOMINAL PAIN LOWER			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COLITIS			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COLITIS ULCERATIVE			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
PYODERMA GANGRENOSUM			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 PNEUMONIA			
subjects affected / exposed	1 / 116 (0.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DENGUE FEVER			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ENTEROCOCCAL INFECTION			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ESCHERICHIA INFECTION			

subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
MALNUTRITION			
subjects affected / exposed	0 / 116 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1: Upadacitinib 45 mg	Part 1: Placebo	Part 2: Upadacitinib 45 mg / Upadacitinib 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 344 (18.02%)	18 / 177 (10.17%)	11 / 68 (16.18%)
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	16 / 344 (4.65%)	2 / 177 (1.13%)	4 / 68 (5.88%)
occurrences (all)	18	2	4
Nervous system disorders			
HEADACHE			
subjects affected / exposed	8 / 344 (2.33%)	9 / 177 (5.08%)	2 / 68 (2.94%)
occurrences (all)	9	10	2
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	8 / 344 (2.33%)	3 / 177 (1.69%)	4 / 68 (5.88%)
occurrences (all)	8	4	4
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	13 / 344 (3.78%)	3 / 177 (1.69%)	4 / 68 (5.88%)
occurrences (all)	13	3	4
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	24 / 344 (6.98%)	3 / 177 (1.69%)	0 / 68 (0.00%)
occurrences (all)	25	3	0

Non-serious adverse events	Part 2: Placebo / Upadacitinib 45 mg		
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 116 (16.38%)		
Investigations BLOOD CREATINE PHOSPHOKINASE INCREASED subjects affected / exposed occurrences (all)	5 / 116 (4.31%) 5		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	2 / 116 (1.72%) 3		
General disorders and administration site conditions PYREXIA subjects affected / exposed occurrences (all)	4 / 116 (3.45%) 4		
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	3 / 116 (2.59%) 3		
Skin and subcutaneous tissue disorders ACNE subjects affected / exposed occurrences (all)	6 / 116 (5.17%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2018	Global amendment 1: • Clarified the study objective to outline both the primary and secondary endpoints. • Enhanced various sections of the protocol to clarify expectations and create better understanding of the content. • Enhanced the description of the DMC review, the contacts list and signatories were updated to reflect changes in study team administration.
24 April 2019	Global amendment 2: • Updating the study objective to include the secondary objectives. • Updating the benefit risk language, modifying exclusion criterion #14 to allow for undetectable biologic levels to be measured via a commercially available assay as an alternative to the washout period, based on regulatory feedback. • Adding the country-specific requirements in the inclusion/exclusion criteria (included 16 and 17-year-old subjects, where locally permitted). • Adding, amending, and clarifying the study procedures. • Adding justification for the use of placebo and further elaborating on the details of the DMC.
29 April 2020	Global amendment 3: • Updated wording about re-testing of exclusionary laboratory values during the screening period. • Clarified intervals for testing biologic drug levels. • Updated the criteria of clinical response for entering extended treatment period for subjects with missing Week 8 endoscopy when endoscopies cannot be performed due to the COVID-19 pandemic. • Moved non-ranked secondary efficacy variables to additional efficacy variables. • Added criteria for failure of ustekinumab treatment, added wording to define borderline serum pregnancy test results, clarified that live vaccines should not be administered for at least 30 days prior to or after study drug administration. • Excluded subjects with a history of gastrointestinal perforation (perforation due to mechanical injury should not exclude a subject from participation). • Prohibited cytapheresis treatment for 60 days prior to screening. • Excluded subjects with prior history of thrombotic events including deep vein thrombosis and pulmonary embolism or known inherited conditions that predispose to hypercoagulability. • Added wording about gastric banding/segmentation to make clear that it is not an exclusion. • Added wording to the washout requirements for all biologic therapies. • Removed wording about women classified as non-childbearing potential. • Updated ECG review requirements. • Updated the type of QuantiFERON TB test used. • Updated toxicity management for aspartate aminotransferase (AST) and alanine aminotransferase (ALT), thrombosis events, and herpes zoster
31 July 2020	Global amendment 4: Updated information on the re-evaluation of the benefit and risk to subjects participating in the study, updated wording to allow for changes in visits and procedures affected by the COVID-19 pandemic and associated changes in global/local regulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported