Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies

Summary

EudraCT number	2017-001240-35
Trial protocol	SK SE DE AT PT BE IE GB LV HU NL PL DK LT EE ES BG HR SI FR IT RO
Global end of trial date	13 January 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	M14-433

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345849
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of Study M14-433 was to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in subjects with moderately and severely active Crohn's disease (CD).

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	China: 66
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Egypt: 27
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 23

Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	South Africa: 20
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 117
Worldwide total number of subjects	526
EEA total number of subjects	119

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)	506
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants with moderately to severely active Crohn’s disease (CD) were randomized at 209 sites in 42 countries. The study consisted of a 12-week double-blind induction treatment period, and a 12-week extended treatment period for participants who did not achieve clinical response at the end of the induction treatment period.

Pre-assignment

Screening details:

In Part 1 participants were randomly assigned in a 2:1 ratio to receive upadacitinib 45 mg or placebo, with randomization stratified by Baseline corticosteroid use (yes or no), endoscopic disease severity (Simple Endoscopic Score for Crohn's disease [SES-CD] < 15 and ≥ 15), and the number of previously failed biologic therapies (0, 1, and >1).

Period 1

Period 1 title	Induction Period (Baseline - Week 12)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once daily for 12 weeks in Part 1.

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:

Taken orally once a day for 12 weeks

Arm title	Upadacitinib 45 mg

Arm description:

Participants received 45 mg upadacitinib once daily for 12 weeks in Part 1.

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:

Taken orally once a day for 12 weeks

Number of subjects in period 1	Placebo	Upadacitinib 45 mg
Started	176	350
Received Study Drug	176	350
Completed	154	330
Not completed	22	20
Consent withdrawn by subject	6	3
Adverse event, non-fatal	8	12
Other	-	1
Lost to follow-up	-	1
Lack of efficacy	8	3

Period 2

Period 2 title	Extended Treatment (Weeks 12-24)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

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

Arm description:

Participants who received placebo during Part 1 and did not achieve clinical response at Week 12 received induction treatment with 45 mg upadacitinib once daily from Week 12 to Week 24.

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:

Taken orally once a day for 12 weeks

Arm title	Upadacitinib 45 mg / Upadacitinib 30 mg

Arm description:

Participants who received upadacitinib during Part 1 and did not achieve clinical response at Week 12 received 30 mg upadacitinib once daily from Week 12 to Week 24.

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:

Taken orally once a day for 12 weeks

Number of subjects in period 2[1]	Placebo / Upadacitinib 45 mg	Upadacitinib 45 mg / Upadacitinib 30 mg
Started	57	59
Completed	49	49
Not completed	8	10
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	2
COVID-19 Logistical Restrictions	1	-
Other	1	1
Coronavirus Disease-2019 (COVID-19) Infection	-	1
Lack of efficacy	1	5

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: Participants who were clinical non-responders at the end of the induction period (Week 12) could enter Part 2.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once daily for 12 weeks in Part 1.	
Reporting group title	Upadacitinib 45 mg
Reporting group description:	
Participants received 45 mg upadacitinib once daily for 12 weeks in Part 1.	

Reporting group values	Placebo	Upadacitinib 45 mg	Total
Number of subjects	176	350	526
Age categorical Units: Subjects			
18 years - < 40 years	91	193	284
40 years - < 65 years	80	142	222
≥ 65 years	5	15	20
Age continuous Units: years			
arithmetic mean	39.3	39.7	
standard deviation	± 13.63	± 13.71	-
Gender categorical Units: Subjects			
Female	82	161	243
Male	94	189	283
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	36	73	109
Black or African American	4	17	21
Native Hawaiian or other Pacific Islander	0	0	0
White	130	258	388
Multiple	6	2	8
Ethnicity Units: Subjects			
Hispanic or Latino	8	27	35
Not Hispanic or Latino	168	323	491
Baseline Corticosteroid Use Units: Subjects			
Yes	64	126	190
No	112	224	336
Number of Previously Failed Biologics			
Zero previously failed biologics includes those who never used biologics previously, and/or who have used and stopped due to reasons other than inadequate response and/or intolerance. Failed treatment includes an inadequate response or intolerance to treatment.			
Units: Subjects			
Zero	98	189	287
One	28	58	86
More than one	50	103	153

Endoscopic Disease Severity			
Endoscopic disease severity was scored using the Simplified Endoscopic Score for Crohn's Disease (SES-CD). The SES-CD evaluates 4 endoscopic variables (ulcer size, ulcerated surface, affected surface, and narrowing, each on a scale from 0 (none) to 3 (worst) in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and ranges from 0 to 56, where higher scores indicate more severe disease.			
Units: Subjects			
SES-CD < 15	110	218	328
SES-CD ≥ 15	66	132	198
Duration of Crohn's Disease Units: years			
arithmetic mean	8.1005	9.2993	
standard deviation	± 7.9901	± 9.4684	-
Crohn's Disease Activity Index (CDAI) Score			
The Crohn's Disease Activity Index (CDAI) is a composite instrument that includes participant symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as physical and laboratory findings. These items are scored individually, weighted, and do not contribute equally to the overall score. The CDAI is derived from summing up the weighted individual scores of eight items. CDAI approximately ranges from 0 to 600 with higher scores indicating more severe disease. Data were available for 176 subjects in the Placebo arm and 349 subjects in the Upadacitinib arm.			
Units: score on a scale			
arithmetic mean	293.85	292.42	
standard deviation	± 85.378	± 81.250	-
Average Daily Abdominal Pain Score			
Participants were asked to rate their abdominal pain on a daily basis in an electronic diary using the following scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The average daily abdominal pain score was calculated using the 4-7 most recent useable days of patient-report outcomes (i.e., excluding days with missing entries or associated with endoscopy procedures) out of the last 14 days prior to the Baseline visit.			
Units: score on a scale			
arithmetic mean	1.9064	1.8917	
standard deviation	± 0.6942	± 0.6795	-
Average Daily Very Soft or Liquid Stool Frequency			
Participants were asked to record the number of very soft or liquid stools on a daily basis in an electronic diary. The average daily very soft or liquid stool frequency was calculated using the 4-7 most recent useable days of patient-report outcomes (i.e., excluding days with missing entries or associated with endoscopy procedures) out of the last 14 days prior to the Baseline visit.			
Units: stools/day			
arithmetic mean	5.0857	5.1864	
standard deviation	± 2.8366	± 2.6130	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once daily for 12 weeks in Part 1.	
Reporting group title	Upadacitinib 45 mg
Reporting group description:	
Participants received 45 mg upadacitinib once daily for 12 weeks in Part 1.	
Reporting group title	Placebo / Upadacitinib 45 mg
Reporting group description:	
Participants who received placebo during Part 1 and did not achieve clinical response at Week 12 received induction treatment with 45 mg upadacitinib once daily from Week 12 to Week 24.	
Reporting group title	Upadacitinib 45 mg / Upadacitinib 30 mg
Reporting group description:	
Participants who received upadacitinib during Part 1 and did not achieve clinical response at Week 12 received 30 mg upadacitinib once daily from Week 12 to Week 24.	

Primary: Percentage of Participants With Clinical Remission Per Patient-Reported Outcomes (PROs) at Week 12

End point title	Percentage of Participants With Clinical Remission Per Patient-Reported Outcomes (PROs) at Week 12

End point description:

The co-primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes was clinical remission based on two patient reported outcomes, average daily SF and average daily APS. Clinical remission per PROs was defined as average daily very soft or liquid SF ≤ 2.8 and average daily APS ≤ 1.0 and neither worse than Baseline.
Participants recorded APS and very soft or liquid SF daily in an electronic diary. Abdominal pain was rated on a scale from 0 (none) to 3 (severe).
The average daily very soft or liquid SF and APS were calculated using the 4-7 most recent useable days of patient-report outcomes (i.e., excluding days with missing entries or associated with endoscopy procedures) out of the last 14 days prior to the Week 12 visit.
Participants with missing data or who withdrew prior to Week 12 were counted as non-responders (non-responder imputation); missing data due to COVID-19 infection or logistical restriction were handled by multiple imputation.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[1]	350[2]		
Units: percentage of participants				
number (confidence interval 95%)	22.2 (16.0 to 28.3)	50.7 (45.5 to 56.0)		

Notes:

[1] - Intention-to-treat (ITT) population includes all randomized subjects who received at least one dose
[2] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	28.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.9
upper limit	36.4

Notes:

[3] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for United States (US)/Food and Drug Administration (FDA) and EU/EMA regulatory purposes.

[4] - Cochran Mantel-Haenszel (CMH) test adjusting for stratification factors (baseline steroid use [Yes, No], endoscopic disease severity [SES-CD < 15, ≥ 15] and number of prior biologics with prior inadequate response or intolerance [0, 1, > 1]).

Primary: Percentage of Participants With Clinical Remission Per Crohn's Disease Activity Index (CDAI) at Week 12

End point title	Percentage of Participants With Clinical Remission Per Crohn's Disease Activity Index (CDAI) at Week 12

End point description:

The co-primary endpoint for United States (US)/Food and Drug Administration (FDA) regulatory purposes was clinical remission based on CDAI at Week 12.
CDAI is a composite instrument that includes participant symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as presence of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever), the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is derived from summing up the weighted individual scores of eight items and ranges approximately from 0 to 600 with higher scores indicating more severe disease. Clinical remission is defined as a CDAI score less than 150.
Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[5]	350[6]		
Units: percentage of participats				
number (confidence interval 95%)	29.1 (22.4 to 35.8)	49.5 (44.2 to 54.8)		

Notes:

[5] - Intention-to-treat population

[6] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	28.8

Notes:

[7] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[8] - Cochran Mantel-Haenszel test adjusting for stratification factors (baseline steroid use [Yes, No], endoscopic disease severity [SES-CD < 15, ≥ 15] and number of prior biologics with prior inadequate response or intolerance [0, 1, > 1]).

Primary: Percentage of Participants With Endoscopic Response at Week 12

End point title	Percentage of Participants With Endoscopic Response at Week 12

End point description:

Endoscopic response at Week 12 was a co-primary endpoint for both the US/FDA and EU/EMA regulatory purposes. Endoscopic response was defined as greater than 50% decrease in Simple Endoscopic Score for Crohn's Disease (SES-CD) from Baseline of the induction study (or for participants with an SES-CD of 4 at Baseline, at least a 2-point reduction from Baseline), as scored by independent external and blinded central readers.

The SES-CD evaluates 4 endoscopic variables (ulcer size, ulcerated surface, affected surface, and narrowing, each on a scale from 0 (none) to 3 in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and ranges from 0 to 56, where higher scores indicate more severe disease. Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[9]	350[10]		
Units: percentage of participants				
number (confidence interval 95%)	13.1 (8.1 to 18.0)	45.5 (40.3 to 50.8)		

Notes:

[9] - Intention-to-treat population

[10] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	33.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.2
upper limit	39.9

Notes:

[11] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[12] - Cochran Mantel-Haenszel test adjusting for stratification factors (baseline steroid use [Yes, No], endoscopic disease severity [SES-CD < 15, ≥ 15] and number of prior biologics with prior inadequate response or intolerance [0, 1, > 1]).

Secondary: Percentage of Participants With Clinical Remission Per PROs at Week 4

End point title	Percentage of Participants With Clinical Remission Per PROs at Week 4

End point description:

Clinical remission per PROs was defined as average daily very soft or liquid SF ≤ 2.8 and average daily APS ≤ 1.0 and neither worse than Baseline.
Participants recorded APS and very soft or liquid SF daily in an electronic diary. Abdominal pain was rated on a scale from 0 (none) to 3 (severe).
The average daily very soft or liquid SF and APS were calculated using the 4-7 most recent useable days of patient-reported outcomes (i.e., excluding days with missing entries or associated with endoscopy procedures) out of the last 14 days prior to the Week 4 visit.
Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[13]	350[14]		
Units: percentage of participants				
number (confidence interval 95%)	14.8 (9.5 to 20.0)	35.7 (30.7 to 40.7)		

Notes:

[13] - Intention-to-treat population

[14] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.3
upper limit	28.2

Notes:

[15] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints. This endpoint was a key secondary endpoint for EU/EMA regulatory purposes.

[16] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants With Endoscopic Remission at Week 12

End point title	Percentage of Participants With Endoscopic Remission at Week 12

End point description:

Endoscopic remission is defined as an SES-CD ≤ 4 and at least 2 point reduction from Baseline and no subscore > 1 in any individual variable,as scored by independent external and blinded central readers. The SES-CD evaluates 4 endoscopic variables (ulcer size, ulcerated surface, affected surface, and narrowing, each on a scale from 0 (none) to 3 in 5 segments assessed during ileocolonoscopy (ileum, right colon, transverse colon, sigmoid and left colon, and rectum). The total score is the sum of the 4 endoscopic variable scores and ranges from 0 to 56, where higher scores indicate more severe disease. Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[17]	350[18]		
Units: percentage of participants				
number (confidence interval 95%)	7.4 (3.5 to 11.3)	28.9 (24.2 to 33.7)		

Notes:

[17] - Intention-to-treat population

[18] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.8
upper limit	27.8

Notes:

[19] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[20] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants Who Discontinued Corticosteroid Use for Crohn's Disease and Achieved Clinical Remission Per PROs at Week 12

End point title	Percentage of Participants Who Discontinued Corticosteroid Use for Crohn's Disease and Achieved Clinical Remission Per PROs at Week 12

End point description:

Corticosteroid-free clinical remission is defined as participants who discontinued corticosteroid use for CD and achieved clinical remission per PROs at Week 12, assessed for participants taking corticosteroids for CD at Baseline.
Clinical remission per PROs was defined as average daily very soft or liquid stool frequency (SF) ≤ 2.8 and average daily APS ≤ 1.0 and neither worse than Baseline.
Participants recorded APS and liquid or very soft SF daily in an electronic diary. Abdominal pain was rated on a scale from 0 (none) to 3 (severe).
The average daily liquid or very soft SF and APS were calculated using the 4-7 most recent useable days of patient-reported outcomes (i.e., excluding days with missing entries or associated with endoscopy procedures) out of the last 14 days prior to the Week 12 visit.
Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[21]	126[22]		
Units: percentage of participants				
number (confidence interval 95%)	12.5 (4.4 to 20.6)	44.4 (35.8 to 53.1)		

Notes:

[21] - Intention-to-treat population; subjects taking corticosteroids for Crohn's disease at Baseline.

[22] - Intention-to-treat population; subjects taking corticosteroids for Crohn's disease at Baseline.

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.0001 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	32.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.5
upper limit	43.7

Notes:

[23] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints. This endpoint was a key secondary endpoint for EU/EMA regulatory purposes.

[24] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) at Week 12

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) at Week 12

End point description:

The FACIT-Fatigue questionnaire is a self-administered patient questionnaire that consists of 13 questions designed to measure the degree of fatigue experienced by participants in the previous 7 days, including physical fatigue (e.g., I feel tired), functional fatigue (e.g., trouble finishing things), emotional fatigue (e.g., frustration), and social consequences of fatigue (e.g., limits social activity). Participants respond to the questions on a scale from 0 (not at all) to 4 (very much). The FACIT-Fatigue score is computed by summing the item scores, after reversing those items that are worded in the negative direction. The FACIT-Fatigue score ranges from 0 to 52, where higher scores represent less fatigue. A positive change from Baseline indicates improvement.
Missing data were handled using a mixed-effect model with repeated measurements (MMRM).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[25]	304[26]		
Units: score on a scale				
least squares mean (confidence interval 95%)	5.0 (3.2 to 6.8)	11.3 (10.0 to 12.5)		

Notes:

[25] - Intention-to-treat population; subjects with non-missing Baseline and Week 12 values.

[26] - Intention-to-treat population; subjects with non-missing Baseline and Week 12 values.

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001 [28]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	8.3

Notes:

[27] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[28] - MMRM model with fixed effects of treatment, visit, and treatment-by-visit interaction, stratification factors, and Baseline value as covariate.

Secondary: Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 12

End point title	Change From Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score at Week 12

End point description:

The Inflammatory Bowel Disease Questionnaire (IBDQ) is used to assess health-related quality of life (HRQoL) in patients with inflammatory bowel disease. 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.
Missing data were handled using a mixed-effect model with repeated measurements (MMRM).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134[29]	304[30]		
Units: score on a scale				
least squares mean (confidence interval 95%)	24.423 (19.007 to 29.840)	46.265 (42.495 to 50.035)		

Notes:

[29] - Intention-to-treat population; participants with non-missing Baseline and Week 12 values.

[30] - Intention-to-treat population; participants with non-missing Baseline and Week 12 values.

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001 [32]
Method	Mixed-effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	21.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.566
upper limit	28.118

Notes:

[31] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[32] - MMRM model with fixed effects of treatment, visit, and treatment-by-visit interaction, stratification factors, and Baseline value as covariate.

Secondary: Percentage of Participants Achieving Clinical Response 100 (CR-100) at Week 2

End point title	Percentage of Participants Achieving Clinical Response 100 (CR-100) at Week 2

End point description:

Clinical response 100 (CR-100) is defined as a decrease of at least 100 points in CDAI from Baseline. CDAI is a composite instrument that includes participant symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as presence of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever), the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is derived from summing up the weighted individual scores of eight items and ranges approximately from 0 to 600 with higher scores indicating more severe disease.

Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 2

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[33]	350[34]		
Units: percentage of participants				
number (confidence interval 95%)	20.4 (14.4 to 26.5)	32.2 (27.3 to 37.1)		

Notes:

[33] - Intention-to-treat population

[34] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Upadacitinib 45 mg v Placebo
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.0022 [36]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	19.2

Notes:

[35] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[36] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants Achieving Clinical Response 100 (CR-100) at Week 12

End point title	Percentage of Participants Achieving Clinical Response 100 (CR-100) at Week 12

End point description:

Clinical response 100 (CR-100) is defined as a decrease of at least 100 points in CDAI from Baseline. CDAI is a composite instrument that includes participant symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as presence of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever), the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is derived from summing up the weighted individual scores of eight items and ranges approximately from 0 to 600 with higher scores indicating more severe disease.

Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[37]	350[38]		
Units: percentage of participants				
number (confidence interval 95%)	37.3 (30.1 to 44.5)	56.6 (51.4 to 61.8)		

Notes:

[37] - Intention-to-treat population

[38] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001 [40]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.3
upper limit	28.4

Notes:

[39] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[40] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants With Hospitalizations Due to Crohn's Disease (CD) During the 12-Week Induction Period

End point title	Percentage of Participants With Hospitalizations Due to Crohn's Disease (CD) During the 12-Week Induction Period

End point description:

This was assessed by reviewing participant's hospitalization data.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[41]	350[42]		
Units: percentage of participants				
number (confidence interval 95%)	5.1 (1.9 to 8.4)	3.7 (1.7 to 5.7)		

Notes:

[41] - Intention-to-treat population

[42] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.4494
Method	Chi-squared
Parameter estimate	Response Rate Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	2.4

Notes:

[43] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

Secondary: Percentage of Participants With Resolution of Extra-Intestinal Manifestation (EIMs) at Week 12

End point title	Percentage of Participants With Resolution of Extra-Intestinal Manifestation (EIMs) at Week 12

End point description:

EIMs are defined as manifestations of Crohn's disease in areas of the body other than the digestive tract, including eyes, skin, joints, mouth, and liver.
Only participants with any EIM present at Baseline were included in the analysis of resolution of EIMs. Resolution of EIMs was defined as absence of all EIMs at the Week 12 visit.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[44]	151[45]		
Units: percentage of participants				
number (confidence interval 95%)	20.9 (11.8 to 30.1)	28.5 (21.3 to 35.7)		

Notes:

[44] - Intention-to-treat population; participants with any EIM at Baseline

[45] - Intention-to-treat population; participants with any EIM at Baseline

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.1044 [47]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	19.9

Notes:

[46] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints, defined separately for US/FDA and EU/EMA regulatory purposes.

[47] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants Who Discontinued Corticosteroid Use for Crohn's Disease and Achieved Clinical Remission Per CDAI at Week 12

End point title	Percentage of Participants Who Discontinued Corticosteroid Use for Crohn's Disease and Achieved Clinical Remission Per CDAI at Week 12

End point description:

Corticosteroid-free clinical remission is defined as participants who discontinued corticosteroid use for CD and achieved clinical remission per CDAI, assessed in participants taking corticosteroids for CD at Baseline.

Clinical remission is defined as CDAI score < 150.

Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[48]	126[49]		
Units: percentage of participants				
number (confidence interval 95%)	15.7 (6.8 to 24.7)	42.9 (34.2 to 51.5)		

Notes:

[48] - Intention-to-treat population; subjects taking corticosteroids for Crohn's disease at Baseline

[49] - Intention-to-treat population; subjects taking corticosteroids for Crohn's disease at Baseline

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	< 0.0001 [51]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	27.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.7
upper limit	39.8

Notes:

[50] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints. This endpoint was a key secondary endpoint for US/FDA regulatory purposes.

[51] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Secondary: Percentage of Participants With Clinical Remission Per CDAI at Week 4

End point title	Percentage of Participants With Clinical Remission Per CDAI at Week 4

End point description:

CDAI is a composite instrument that includes participant symptoms evaluated over 7 days (abdominal pain, stool frequency and general well-being), as well as presence of complications (arthritis/arthralgia, iritis/uveitis, erythema nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure/fistula/abscess, other fistula, and fever), the use of antidiarrheal medicines, presence of an abdominal mass, hematocrit, and body weight. The CDAI is derived from summing up the weighted individual scores of eight items and ranges from approximately 0 to 600 with higher scores indicating more severe disease. Clinical remission is defined as CDAI score less than 150.
Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 infection or logistical restriction was used in the analysis.

End point type	Secondary

End point timeframe:

Week 4

End point values	Placebo	Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176[52]	350[53]		
Units: percentage of participants				
number (confidence interval 95%)	26.7 (20.2 to 33.3)	37.1 (32.1 to 42.2)		

Notes:

[52] - Intention-to-treat population

[53] - Intention-to-treat population

Statistical analyses

Statistical analysis title	Treatment Difference
Comparison groups	Placebo v Upadacitinib 45 mg
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.0071 [55]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Response Rate Difference
Point estimate	10.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	18.6

Notes:

[54] - The overall type I error rate of the co-primary and key secondary endpoints were strongly controlled using a fixed sequence multiple-testing procedure as well as a Holm procedure. The testing utilized the sequence of hypothesis testing for the co-primary endpoints using two-sided α of 0.05 followed by a set of key secondary endpoints. This endpoint was a key secondary endpoint for US/FDA regulatory purposes.

[55] - Cochran Mantel-Haenszel test adjusted for stratification factors.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Part 1: 12 weeks; Part 2: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Part 1: Placebo
Reporting group description: Participants received placebo once daily for 12 weeks in Part 1.	
Reporting group title	Part 1: Upadacitinib 45 mg
Reporting group description: Participants received 45 mg upadacitinib once daily for 12 weeks in Part 1.	
Reporting group title	Part 2: Placebo / Upadacitinib 45 mg
Reporting group description: Participants who received placebo during Part 1 and did not achieve clinical response at Week 12 received induction treatment with 45 mg upadacitinib once daily from Week 12 to Week 24.	
Reporting group title	Part 2: Upadacitinib 45 mg / Upadacitinib 30 mg
Reporting group description: Participants who received upadacitinib during Part 1 and did not achieve clinical response at Week 12 received 30 mg upadacitinib once daily from Week 12 to Week 24.	

Serious adverse events	Part 1: Placebo	Part 1: Upadacitinib 45 mg	Part 2: Placebo / Upadacitinib 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 176 (6.82%)	24 / 350 (6.86%)	4 / 57 (7.02%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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
PARAESTHESIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
ANAL FISTULA			

subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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
CONSTIPATION			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
CROHN'S DISEASE			
subjects affected / exposed	5 / 176 (2.84%)	7 / 350 (2.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 5	1 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTERITIS			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	0 / 57 (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
ILEAL STENOSIS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
ILEUS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 176 (0.00%)	2 / 350 (0.57%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINAL STENOSIS			

subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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 GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
METASTATIC CUTANEOUS CROHN'S DISEASE			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			

subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	0 / 57 (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
NEPHROLITHIASIS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
Musculoskeletal and connective tissue disorders			
FLANK PAIN			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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			
ANAL ABSCESS			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (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
APPENDICITIS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
COVID-19			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	0 / 57 (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			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS ROTAVIRUS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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

GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	0 / 57 (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
OSTEOMYELITIS			
subjects affected / exposed	1 / 176 (0.57%)	0 / 350 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL ABSCESS			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
PNEUMONIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 176 (0.00%)	0 / 350 (0.00%)	0 / 57 (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
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 176 (0.00%)	1 / 350 (0.29%)	0 / 57 (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

Serious adverse events	Part 2: Upadacitinib 45 mg / Upadacitinib 30 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 59 (10.17%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
FALL			

subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PARAESTHESIA			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SEIZURE			
subjects affected / exposed	0 / 59 (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 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ANAL FISTULA			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CONSTIPATION			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CROHN'S DISEASE			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ENTERITIS			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ILEAL STENOSIS			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ILEUS			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
INTESTINAL PERFORATION			

subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LARGE INTESTINAL STENOSIS				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LARGE INTESTINE PERFORATION				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
LOWER GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS ACUTE				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
ACUTE RESPIRATORY FAILURE				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
METASTATIC CUTANEOUS CROHN'S DISEASE				

subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
NEPHROLITHIASIS			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
FLANK PAIN			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
APPENDICITIS			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 59 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

GASTROENTERITIS ROTAVIRUS				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTROENTERITIS VIRAL				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
OSTEOMYELITIS				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
RECTAL ABSCESS				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	0 / 59 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 59 (1.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
HYPOKALAEMIA				
subjects affected / exposed	0 / 59 (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: Placebo	Part 1: Upadacitinib 45 mg	Part 2: Placebo / Upadacitinib 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 176 (21.02%)	93 / 350 (26.57%)	14 / 57 (24.56%)
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	8 / 176 (4.55%)	21 / 350 (6.00%)	3 / 57 (5.26%)
occurrences (all)	8	23	3
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 176 (1.14%)	14 / 350 (4.00%)	1 / 57 (1.75%)
occurrences (all)	2	15	1
Gastrointestinal disorders			
CROHN'S DISEASE			
subjects affected / exposed	13 / 176 (7.39%)	6 / 350 (1.71%)	1 / 57 (1.75%)
occurrences (all)	13	6	1
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 176 (0.57%)	24 / 350 (6.86%)	3 / 57 (5.26%)
occurrences (all)	1	24	3
RASH			
subjects affected / exposed	4 / 176 (2.27%)	13 / 350 (3.71%)	3 / 57 (5.26%)
occurrences (all)	4	14	3
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	8 / 176 (4.55%)	9 / 350 (2.57%)	3 / 57 (5.26%)
occurrences (all)	9	10	3
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 176 (0.00%)	3 / 350 (0.86%)	3 / 57 (5.26%)
occurrences (all)	0	3	3
NASOPHARYNGITIS			
subjects affected / exposed	6 / 176 (3.41%)	16 / 350 (4.57%)	2 / 57 (3.51%)
occurrences (all)	6	16	2

Non-serious adverse events	Part 2: Upadacitinib 45 mg / Upadacitinib 30 mg		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	13 / 59 (22.03%)		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Gastrointestinal disorders			
CROHN'S DISEASE			
subjects affected / exposed	3 / 59 (5.08%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
RASH			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences (all)	1		
NASOPHARYNGITIS			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2017	Major changes to the protocol included: • Updated eligibility criteria. • Updated the duration of the maintenance part of Substudy 1 from 48 to 52 weeks. • Revised ranked secondary and additional secondary efficacy endpoints.
24 January 2018	Major changes to the protocol included: • Added vedolizumab as a prohibited biologic therapy during the study. • Clarified that the primary variables would be analyzed for subjects enrolled in Part 1. • Clarified that the secondary variables would be analyzed for subjects enrolled in Part 1. • Clarification on the analysis methods considered for continuous secondary endpoints.
24 August 2018	Major changes to the protocol included: • Minimum screening period duration was corrected and rescreening process was clarified. • Updated eligibility criteria. • Clarified and provided additional guidance on the use of concomitant corticosteroids. • Updated and clarified prohibited therapies. • Corrected and updated contraception recommendations. • Added the Montreal classification for CD at Screening. • Revised ranked secondary and additional secondary efficacy endpoints. • Updated the list of adverse events of special interest (AESIs). • Removed Section 6.1.3.1. • Reduced the number of data point collections of the Crohn's Symptom Severity (CSS) during the study.
08 April 2019	Major chnages to the protocol included: • Revised study title. • Updated Section 5.1 and Section 5.3.1.1 for alignment with induction Study M14-431 to include enrollment of Bio-IR subjects which increased the subject population. • Updated eligibility criteria. • Corrected and updated contraception recommendations. • Revised ranked secondary and additional secondary efficacy endpoints.
29 April 2020	Major changes to the protocol included: • Removed the number of subjects and the maximum enrollment in the subpopulations. • Included COVID-19 pandemic provisions for post-baseline endoscopy. • Updated eligibility criteria. • Revised prohibited therapy. • Removed eGFR at Week 12 and Week 24. • Increased the number of intestinal biopsy samples to be collected. • Changed co-primary efficacy endpoint to clinical remission based on CDAI for the US/FDA. • Revised ranked secondary and additional secondary efficacy endpoints. • Updated the AESIs.

24 September 2020	Major changes to the protocol included: • 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 COVID-19 pandemic and asocial changes in global/local regulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported