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 Biologic Therapy

Summary

EudraCT number	2017-001226-18
Trial protocol	SK SE DK AT PT BE IE GB LV HU DE PL CZ LT EE ES BG SI HR IT RO
Global end of trial date	11 August 2021

Results information

Result version number	v1 (current)
This version publication date	03 August 2022
First version publication date	03 August 2022

Trial information

Trial identification

Sponsor protocol code	M14-431

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345836
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	11 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in participants with moderately and severely active Crohn’s disease (CD).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 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	Puerto Rico: 3
Country: Number of subjects enrolled	United States: 180
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Egypt: 8
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 8
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	China: 55
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Argentina: 3

Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Estonia: 3
Worldwide total number of subjects	624
EEA total number of subjects	176

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)	603
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study had 3 Parts: Part 1: A randomized, double-blind, placebo-controlled Induction Period, Part 2: A single-arm active Induction Period to receive upadacitinib. Part 3: An Extended Treatment Period for clinical non-responders from Parts 1 or 2.

Pre-assignment

Screening details:

Once the enrollment for Part 1 was complete, participants were further enrolled in an open-label, single-arm active Induction Period to receive upadacitinib.in Part 2. Part 3 has 3 cohorts: Cohorts 1 and 2 included participants who received placebo and upadacitinib in Part 1, respectively; Cohort 3 included participants from Part 2.

Period 1

Period 1 title	DB and OL Induction (12 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Blinding implementation details:

Blinding was applicable only to Part 1 where participants received upadacitinib 45 mg once daily (QD) or matching placebo for 12 weeks in a double-blind (DB) way. Part 2 was implemented in a non-blinded manner, with participants receiving open label (OL) upadacitinib 45 mg QD for 12 weeks.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 (DB): Placebo

Arm description:

Participants received upadacitinib matching placebo tablets, orally, once daily (QD) for 12 weeks during the Double-blind (DB) Induction Period.

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:

Upadacitinib matching placebo tablets, orally

Arm title	Part 1 (DB): Upadacitinib 45 mg

Arm description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the DB Induction Period.

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

Dosage and administration details:

Upadacitinib 45 mg tablets, orally

Arm title	Part 2 (OL): Upadacitinib 45 mg

Arm description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the Open-label (OL) Induction Period.

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

Dosage and administration details:

Upadacitinib 45 mg tablets, orally

Number of subjects in period 1	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg	Part 2 (OL): Upadacitinib 45 mg
Started	171	324	129
Completed	149	291	123
Not completed	22	33	6
Adverse event	5	17	2
Withdrew consent	8	8	3
Reason not specified	1	3	1
Lost to follow-up	-	1	-
Lack of efficacy	8	4	-

Period 2

Period 2 title	12-Week Extended Treatment (ET)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Blinding implementation details:

Participants from Part 1 arm groups remained blinded to treatment in Part 3 to avoid unmasking the treatment received during Part 1. Participants from Part 2 arm group received OL treatment in Part 3.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo

Arm description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks (until Week 24) during the Extended Treatment (ET) Period. Participants who received placebo in Part 1 and did not achieve clinical response at Week 12 were included in this group.

Arm type	Experimental

Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Upadacitinib 45 mg tablets, orally

Arm title	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib 45mg

Arm description:

Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the ET Period. Participants who received DB upadacitinib 45 mg in Part 1 and did not achieve clinical response at Week 12 were included in this group.

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

Dosage and administration details:

Upadacitinib 30 mg tablets, orally

Arm title	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg

Arm description:

Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the ET Period. Participants who received OL upadacitinib 45 mg during Part 2 and did not achieve clinical response at Week 12 were included in this group.

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

Dosage and administration details:

Upadacitinib 30 mg tablets, orally

Number of subjects in period 2[1]	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib 45mg	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg
Started	78	69	14
Completed	67	51	8
Not completed	11	18	6
Adverse event	8	5	-
COVID-19 logistical restrictions	-	1	-
Reason not specified	1	1	1
Withdrew consent	-	5	1
Lost to follow-up	-	-	1
Lack of efficacy	2	6	3

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: Subjects included as 'Completed' in Period 1=completed study. Non-responders from Parts 1 or 2 were enroled into the Extended Treatment Period (Part 3).

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 (DB): Placebo
Reporting group description:	
Participants received upadacitinib matching placebo tablets, orally, once daily (QD) for 12 weeks during the Double-blind (DB) Induction Period.	
Reporting group title	Part 1 (DB): Upadacitinib 45 mg
Reporting group description:	
Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the DB Induction Period.	
Reporting group title	Part 2 (OL): Upadacitinib 45 mg
Reporting group description:	
Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the Open-label (OL) Induction Period.	

Reporting group values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg	Part 2 (OL): Upadacitinib 45 mg
Number of subjects	171	324	129
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	37.5	38.4	39.1
full range (min-max)	18 to 74	18 to 73	18 to 68
Gender categorical			
Units: Subjects			
Female	75	155	60
Male	96	169	69
Ethnicity			
Units: Subjects			
Hispanic or Latino	8	24	8
Not Hispanic or Latino	163	300	121
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	38	69	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	19	5
White	126	230	113
More than one race	0	5	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	624		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	290		
Male	334		
Ethnicity Units: Subjects			
Hispanic or Latino	40		
Not Hispanic or Latino	584		
Unknown or Not Reported	0		
Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	118		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	30		
White	469		
More than one race	5		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Part 1 (DB): Placebo
Reporting group description:	
Participants received upadacitinib matching placebo tablets, orally, once daily (QD) for 12 weeks during the Double-blind (DB) Induction Period.	
Reporting group title	Part 1 (DB): Upadacitinib 45 mg
Reporting group description:	
Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the DB Induction Period.	
Reporting group title	Part 2 (OL): Upadacitinib 45 mg
Reporting group description:	
Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the Open-label (OL) Induction Period.	
Reporting group title	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo
Reporting group description:	
Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks (until Week 24) during the Extended Treatment (ET) Period. Participants who received placebo in Part 1 and did not achieve clinical response at Week 12 were included in this group.	
Reporting group title	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib 45mg
Reporting group description:	
Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the ET Period. Participants who received DB upadacitinib 45 mg in Part 1 and did not achieve clinical response at Week 12 were included in this group.	
Reporting group title	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg
Reporting group description:	
Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the ET Period. Participants who received OL upadacitinib 45 mg during Part 2 and did not achieve clinical response at Week 12 were included in this group.	

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[1]
End point description:	
Clinical remission per PROs was defined as average daily very soft or liquid stool frequency (SF) ≤2.8 and average daily abdominal pain (AP) score ≤1.0 and both not greater than Baseline. The number of soft or liquid stools and abdominal pain rated on a scale of 0=none to 3=severe were recorded in an electronic diary. Results were based on non-responder imputation incorporating multiple imputation to handle missing data due to coronavirus disease (COVID-19) [NRI-C]. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1.	

End point type	Primary
End point timeframe:	
Baseline to Week 12	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	14.0 (8.8 to 19.2)	39.8 (34.5 to 45.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	25.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.7
upper limit	33.1

Notes:

[2] - Point estimate and 95% CI were calculated using CMH.

[3] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Primary: Percentage of Participants With Endoscopic Response at Week 12

End point title	Percentage of Participants With Endoscopic Response at Week 12[4]

End point description:

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 of the induction study, at least a 2-point reduction from Baseline), as scored by Central Reviewer. SES-CD is calculated based the sum of individual segment values for four endoscopic variables (presence and size of ulcers, ulcerated surface, affected surface and presence of narrowing). Each variable in each segment is scored 0 to 3 resulting in SES-CD values ranging from 0 to 56 with higher scores indicating more severe disease. Intent-to-Treat (ITT)1 Population included all randomised participants who received at least one dose of DB study drug during Part 1. Results were based on NRI-C.

End point type	Primary

End point timeframe:

Baseline to Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	3.5 (0.8 to 6.3)	34.6 (29.4 to 39.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	31.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.5
upper limit	37

Notes:

[5] - Point estimate and 95% confidence interval (CI) were calculated using Cochran-Mantel-Haenszel test (CMH).

[6] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Primary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events[7]

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Safety Population for Part 1 (SA1)=all participants who received at least one dose of the study drug in Part 1, SA2=all participants who received at least one dose of the study drug in Part 2, and SA3=all participants who received at least one dose of the study drug (upadacitinib 30 mg or upadacitinib 45 mg) in Part 3.

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days following last dose of study drug (up to approximately 28 weeks)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses are reported for this endpoint.

End point values	Part 1 (DB): Placebo	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo	Part 1 (DB): Upadacitinib 45 mg	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib 45mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	171	78	324	69
Units: participants	112	53	221	45

End point values	Part 2 (OL): Upadacitinib 45 mg	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	14		
Units: participants	86	9		

Statistical analyses

No statistical analyses for this end point

Secondary: 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[8]

End point description:

The CDAI was used to evaluate the activity of Crohn's disease. Clinical remission per CDAI is defined as CDAI <150. The CDAI is calculated on the basis of a one-week evaluation of 8 items: frequency of liquid or very soft stool, abdominal pain, complications of Crohn's disease (e.g., uveitis, arthritis, fistula, and abscess), abdominal mass, hematocrit, body weight, use of antidiarrheals, and general condition. Total score ranges from 0 to 600. Higher CDAI scores indicate more severe disease. CDAI scores below 150 represent remission and scores over 450 represent very severe Crohn's disease. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1. Results were based on NRI-C.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	21.1 (14.9 to 27.2)	38.9 (33.6 to 44.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Risk Difference
Point estimate	17.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	25.8

Notes:

[9] - Point estimate and 95% CI were calculated using CMH risk difference estimate.

[10] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Secondary: Percentage of Participants With Clinical Remission Per Patient Reported Outcomes (PROs) at Week 4

End point title	Percentage of Participants With Clinical Remission Per Patient Reported Outcomes (PROs) at Week 4[11]

End point description:

Clinical remission per PROs was defined as average daily very soft or liquid stool frequency (SF) ≤2.8 and average daily abdominal pain (AP) score ≤1.0 and both not greater than Baseline. The number of soft or liquid stools and abdominal pain rated on a scale of 0=none to 3=severe were recorded in an electronic diary. Results were based on NRI-C. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	9.4 (5.0 to 13.7)	32.4 (27.3 to 37.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001 [13]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	23.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.6
upper limit	29.9

Notes:

[12] - Point estimate and 95% CI were calculated using CMH.

[13] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Secondary: Percentage of Participants With Endoscopic Remission at Week 12

End point title	Percentage of Participants With Endoscopic Remission at Week 12[14]

End point description:

Endoscopic remission was defined per SES-CD. SES-CD ≤4 and at least 2-point reduction from Baseline and no subscore >1 in any individual variable, as scored by Central Reviewer. SES-CD is calculated based the sum of individual segment values for four endoscopic variables (presence and size of ulcers, ulcerated surface, affected surface and presence of narrowing). Each variable in each segment is scored 0 to 3 resulting in SES-CD values ranging from 0 to 56 with higher scores indicating more severe disease. Results were based on NRI-C. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1.

End point type	Secondary

End point timeframe:

Baseline to Week 12

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	2.3 (0.1 to 4.6)	19.1 (14.9 to 23.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	12
upper limit	21.6

Notes:

[15] - Point estimate and 95% CI were calculated using CMH.

[16] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Secondary: Percentage of Participants who Discontinued Corticosteroid Use for Crohn's Disease (CD) and Achieved Clinical Remission per PROs at Week 12, in Participants Taking Corticosteroids at Baseline

End point title	Percentage of Participants who Discontinued Corticosteroid Use for Crohn's Disease (CD) and Achieved Clinical Remission per PROs at Week 12, in Participants Taking Corticosteroids at Baseline[17]

End point description:

Clinical remission per PROs was defined as average daily very soft or liquid stool frequency (SF) ≤2.8 and average daily abdominal pain (AP) score ≤1.0 and both not greater than Baseline. The number of soft or liquid stools and abdominal pain rated on a scale of 0=none to 3=severe were recorded in an electronic diary. Results were based on NRI-C. ITT1 Population=participants receiving at least one dose of DB study drug during Part 1. Number of subjects analysed=number of participants who were taking corticosteroids at Baseline.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	108		
Units: percentage of participants				
number (confidence interval 95%)	6.7 (0.4 to 13.0)	37.0 (27.9 to 46.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.0001 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.4
upper limit	41

Notes:

[18] - Point estimate and 95% CI were calculated using CMH.

[19] - P-value was calculated using CMH test adjusted for randomisation stratification factors.

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

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Total Score at Week 12[20]

End point description:

The FACIT-F questionnaire was developed to assess fatigue associated with anemia. It consists of 13 fatigue-related questions. The responses to the 13 items on the FACIT-F questionnaire are each measured on a 5-point Likert scale. The responses to the answers are the following: 0= not at all; 1= a little bit; 2= somewhat; 3= quite a bit; 4=very much. Thus, the total score ranges from 0 to 52. High scores represent less fatigue. A positive change from Baseline indicates improvement. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1. Overall number of subjects analyzed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	278		
Units: score on a scale				
least squares mean (standard error)	3.9 (± 0.97)	11.4 (± 0.69)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001 [22]
Method	MMRM
Parameter estimate	Adjusted Treatment Difference
Point estimate	7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	9.8

Notes:

[21] - Point estimate and 95% CI were calculated using MMRM.

[22] - P-value was calculated using MMRM with Baseline, treatment, visit, treatment by visit interaction and stratification factors in the model.

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[23]

End point description:

The IBDQ is a disease-specific instrument composed of 32 Likert-scaled items. The IBDQ scale contains 4 component subscales: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function(5 items). Each item is scored on a 7-point scale where: 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. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1. Overall number of subjects analyzed are the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	280		
Units: score on a scale				
least squares mean (standard error)	21.6 (± 3.02)	46.0 (± 2.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.0001 [25]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted Treatment Difference
Point estimate	24.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.2
upper limit	31.5

Notes:

[24] - Point estimate and 95% CI were calculated using MMRM.

[25] - P-value was calculated using MMRM with Baseline, treatment, visit, treatment by visit interaction and stratification factors in the model.

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[26]

End point description:

CR-100 is defined as a decrease of at least 100 points in CDAI from Baseline at week 2. The CDAI is used to evaluate the activity of Crohn's disease. The CDAI is calculated on the basis of a one-week evaluation of 8 items: frequency of liquid or very soft stool, abdominal pain, complications of Crohn's disease (e.g., uveitis, arthritis, fistula, and abscess), abdominal mass, hematocrit, body weight, use of antidiarrheals, and general condition. Total score ranges from 0 to about 600. Higher CDAI scores indicate more severe disease. CDAI scores below 150 represent remission and scores over 450 represent very severe Crohn's disease. Results were based on NRI-C. ITT1 Population included all randomized participants who received at least one dose of DB study drug during Part 1.

End point type	Secondary

End point timeframe:

Baseline to Week 2

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	12.4 (7.4 to 17.4)	33.2 (28.0 to 38.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.0001 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.7
upper limit	27.8

Notes:

[27] - Point estimate and 95% CI were calculated using CMH.

[28] - P-value was calculated using CMH test adjusted for randomization 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[29]

End point description:

CR-100 is defined as a decrease of at least 100 points in CDAI from Baseline at Week 12. The CDAI is used to evaluate the activity of Crohn's disease. The CDAI is calculated on the basis of a one-week evaluation of 8 items: frequency of liquid or very soft stool, abdominal pain, complications of Crohn's disease (e.g., uveitis, arthritis, fistula, and abscess), abdominal mass, hematocrit, body weight, use of antidiarrheals, and general condition. Total score ranges from 0 to about 600. Higher CDAI scores indicate more severe disease. CDAI scores below 150 represent remission and scores over 450 represent very severe Crohn's disease. Results were based on NRI-C. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1.

End point type	Secondary

End point timeframe:

Baseline to Week 12

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	27.5 (20.8 to 34.2)	50.5 (45.1 to 56.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.0001 [31]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.4
upper limit	31.2

Notes:

[30] - Point estimate and 95% CI were calculated using CMH.

[31] - P-value was calculated using CMH test adjusted for randomization stratification factors.

Secondary: Percentage of Participants With Hospitalizations Due to Crohn's Disease (CD) During Part 1 (12-week Double-blind Induction Period)

End point title	Percentage of Participants With Hospitalizations Due to Crohn's Disease (CD) During Part 1 (12-week Double-blind Induction Period)[32]

End point description:

ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1.

End point type	Secondary

End point timeframe:

Up to Week 12 in Part 1: Double-blind Induction Period

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	324		
Units: percentage of participants				
number (confidence interval 95%)	8.8 (4.5 to 13.0)	6.2 (3.6 to 8.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.2834 [34]
Method	Chi-squared
Parameter estimate	Treatment Difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	2.4

Notes:

[33] - Point estimate and 95% CI were calculated using Chi-squared test.

[34] - P-value was calculated using Chi-squared test.

Secondary: Percentage of Participants With Resolution of Extra-Intestinal Manifestations (EIMs) at Week 12, in Participants With EIMs at Baseline

End point title	Percentage of Participants With Resolution of Extra-Intestinal Manifestations (EIMs) at Week 12, in Participants With EIMs at Baseline[35]

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. ITT1 Population included all randomised participants who received at least one dose of DB study drug during Part 1. Number of subjects analysed is the number of participants with any EIMs at Baseline.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only Part 1 Double-blind arms are applicable to this endpoint.

End point values	Part 1 (DB): Placebo	Part 1 (DB): Upadacitinib 45 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	131		
Units: percentage of participants				
number (confidence interval 95%)	21.7 (11.2 to 32.1)	32.8 (24.8 to 40.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1 (DB): Placebo v Part 1 (DB): Upadacitinib 45 mg
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0833 [37]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	24.4

Notes:

[36] - Point estimate and 95% CI were calculated using CMH.

[37] - P-value was calculated using CMH test adjusted for randomisation stratification factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days following last dose of study drug (up to approximately 28 weeks)

Adverse event reporting additional description:

Safety Population for Part 1 (SA1)=all participants who received at least one dose of the study drug in Part 1,SA2=all participants who received at least one dose of the study drug in Part 2, and SA3=all participants who received at least one dose of the study drug (upadacitinib 30 mg or upadacitinib 45 mg) in Part 3.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Part 1 (Double Blind): Upadacitinib 45 mg

Reporting group description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the Double-blind Induction Period.

Reporting group title	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg

Reporting group description:

Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the Extended Treatment Period. Participants who received OL upadacitinib 45 mg during Part 2 and did not achieve clinical response at Week 12 were included in this group.

Reporting group title	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo

Reporting group description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks (until Week 24) during the Extended Treatment Period. Participants who received placebo in Part 1 and did not achieve clinical response at Week 12 were included in this group.

Reporting group title	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib 45mg

Reporting group description:

Participants received upadacitinib 30 mg tablets, orally, QD for 12 weeks (until Week 24) during the Extended Treatment Period. Participants who received DB upadacitinib 45 mg in Part 1 and did not achieve clinical response at Week 12 were included in this group.

Reporting group title	Part 1 (Double Blind): Placebo

Reporting group description:

Participants received upadacitinib matching placebo tablets, orally, QD for 12 weeks during the Double-blind Induction Period.

Reporting group title	Part 2 (Open Label): Upadacitinib 45 mg

Reporting group description:

Participants received upadacitinib 45 mg tablets, orally, QD for 12 weeks during the Open-label Induction Period.

Serious adverse events	Part 1 (Double Blind): Upadacitinib 45 mg	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 324 (9.26%)	5 / 14 (35.71%)	11 / 78 (14.10%)

number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
UTERINE POLYP			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Respiratory, thoracic and mediastinal disorders			
LUNG DISORDER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG ABUSE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
DRUG USE DISORDER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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

PSYCHOTIC DISORDER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE ILEUS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
LEUKOPENIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
Ear and labyrinth disorders			
VERTIGO			

subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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 PAIN			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
CONSTIPATION			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
CROHN'S DISEASE			
subjects affected / exposed	7 / 324 (2.16%)	3 / 14 (21.43%)	3 / 78 (3.85%)
occurrences causally related to treatment / all	1 / 7	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCUTANEOUS FISTULA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	3 / 324 (0.93%)	0 / 14 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHEZIA			

subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
HAEMORRHOIDS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEAL PERFORATION			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
INTESTINAL STENOSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
SMALL INTESTINAL OBSTRUCTION			

subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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			
CHOLELITHIASIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
URETEROLITHIASIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Musculoskeletal and connective tissue disorders			
ANKYLOSING SPONDYLITIS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 14 (7.14%)	0 / 78 (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
ABDOMINAL WALL ABSCESS			

subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
ANAL ABSCESS			
subjects affected / exposed	3 / 324 (0.93%)	0 / 14 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 14 (7.14%)	0 / 78 (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 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (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
PNEUMOCYSTIS JIROVECII PNEUMONIA			

subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
RETROPERITONEAL ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
Metabolism and nutrition disorders			
GOUT			
subjects affected / exposed	1 / 324 (0.31%)	0 / 14 (0.00%)	0 / 78 (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
HYPOKALAEMIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 14 (7.14%)	0 / 78 (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
TYPE 1 DIABETES MELLITUS			

subjects affected / exposed	0 / 324 (0.00%)	0 / 14 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib	Part 1 (Double Blind): Placebo	Part 2 (Open Label): Upadacitinib 45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 69 (10.14%)	17 / 171 (9.94%)	9 / 129 (6.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
UTERINE POLYP			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
LUNG DISORDER			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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

DRUG ABUSE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
DRUG USE DISORDER			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
POSTOPERATIVE ILEUS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 69 (1.45%)	0 / 171 (0.00%)	0 / 129 (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

LEUKOPENIA			
subjects affected / exposed	1 / 69 (1.45%)	0 / 171 (0.00%)	0 / 129 (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
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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 UPPER			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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
CONSTIPATION			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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
CROHN'S DISEASE			
subjects affected / exposed	4 / 69 (5.80%)	10 / 171 (5.85%)	4 / 129 (3.10%)
occurrences causally related to treatment / all	0 / 5	0 / 13	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCUTANEOUS FISTULA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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

GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHEZIA			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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
HAEMORRHOIDS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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 PERFORATION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
ILEUS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
INTESTINAL PERFORATION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
INTESTINAL STENOSIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
PANCREATITIS ACUTE			

subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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 / 69 (1.45%)	0 / 171 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 69 (1.45%)	0 / 171 (0.00%)	0 / 129 (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
URETEROLITHIASIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
Musculoskeletal and connective tissue disorders			
ANKYLOSING SPONDYLITIS			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			

subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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 WALL ABSCESS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL ABSCESS			
subjects affected / exposed	0 / 69 (0.00%)	2 / 171 (1.17%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC ABSCESS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	1 / 129 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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	0 / 69 (0.00%)	0 / 171 (0.00%)	2 / 129 (1.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
GASTROENTERITIS VIRAL			

subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
RETROPERITONEAL ABSCESS			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
SEPTIC SHOCK			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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			
GOUT			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
HYPOKALAEMIA			

subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (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
TYPE 1 DIABETES MELLITUS			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	0 / 129 (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

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

Non-serious adverse events	Part 1 (Double Blind): Upadacitinib 45 mg	Part3(ET OL):Upadacitinib 30mg From Part2 OL Upadacitinib 45mg	Part 3 (ET DB): Upadacitinib 45 mg From Part 1 DB Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 324 (38.89%)	7 / 14 (50.00%)	29 / 78 (37.18%)
Investigations			
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	1 / 324 (0.31%)	1 / 14 (7.14%)	0 / 78 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	20 / 324 (6.17%)	0 / 14 (0.00%)	2 / 78 (2.56%)
occurrences (all)	24	0	2
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	16 / 324 (4.94%)	0 / 14 (0.00%)	3 / 78 (3.85%)
occurrences (all)	17	0	3
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	13 / 324 (4.01%)	0 / 14 (0.00%)	4 / 78 (5.13%)
occurrences (all)	13	0	4
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	9 / 324 (2.78%)	0 / 14 (0.00%)	3 / 78 (3.85%)
occurrences (all)	10	0	3
CONSTIPATION			

subjects affected / exposed	7 / 324 (2.16%)	0 / 14 (0.00%)	1 / 78 (1.28%)
occurrences (all)	7	0	1
CROHN'S DISEASE			
subjects affected / exposed	12 / 324 (3.70%)	1 / 14 (7.14%)	5 / 78 (6.41%)
occurrences (all)	12	1	5
NAUSEA			
subjects affected / exposed	15 / 324 (4.63%)	2 / 14 (14.29%)	3 / 78 (3.85%)
occurrences (all)	15	2	3
VOMITING			
subjects affected / exposed	8 / 324 (2.47%)	2 / 14 (14.29%)	0 / 78 (0.00%)
occurrences (all)	8	2	0
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	15 / 324 (4.63%)	0 / 14 (0.00%)	5 / 78 (6.41%)
occurrences (all)	16	0	5
ALOPECIA			
subjects affected / exposed	3 / 324 (0.93%)	1 / 14 (7.14%)	0 / 78 (0.00%)
occurrences (all)	3	1	0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 14 (7.14%)	0 / 78 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	5 / 324 (1.54%)	1 / 14 (7.14%)	1 / 78 (1.28%)
occurrences (all)	5	1	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	7 / 324 (2.16%)	0 / 14 (0.00%)	2 / 78 (2.56%)
occurrences (all)	7	0	2
BACK PAIN			
subjects affected / exposed	4 / 324 (1.23%)	0 / 14 (0.00%)	2 / 78 (2.56%)
occurrences (all)	4	0	2
FISTULA DISCHARGE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 14 (7.14%)	0 / 78 (0.00%)
occurrences (all)	0	1	0

Infections and infestations			
INFLUENZA			
subjects affected / exposed	9 / 324 (2.78%)	1 / 14 (7.14%)	2 / 78 (2.56%)
occurrences (all)	10	1	2
FOLLICULITIS			
subjects affected / exposed	5 / 324 (1.54%)	0 / 14 (0.00%)	5 / 78 (6.41%)
occurrences (all)	5	0	5
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	17 / 324 (5.25%)	0 / 14 (0.00%)	2 / 78 (2.56%)
occurrences (all)	18	0	3
NASOPHARYNGITIS			
subjects affected / exposed	23 / 324 (7.10%)	0 / 14 (0.00%)	3 / 78 (3.85%)
occurrences (all)	24	0	4

Non-serious adverse events	Part3(ET DB):Upadacitinib 30mg From Part1 DB Upadacitinib	Part 1 (Double Blind): Placebo	Part 2 (Open Label): Upadacitinib 45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 69 (17.39%)	69 / 171 (40.35%)	44 / 129 (34.11%)
Investigations			
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	1 / 129 (0.78%)
occurrences (all)	0	0	1
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 69 (0.00%)	9 / 171 (5.26%)	8 / 129 (6.20%)
occurrences (all)	0	10	8
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 69 (1.45%)	9 / 171 (5.26%)	6 / 129 (4.65%)
occurrences (all)	1	12	6
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	1 / 69 (1.45%)	8 / 171 (4.68%)	4 / 129 (3.10%)
occurrences (all)	1	8	5
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed	0 / 69 (0.00%)	12 / 171 (7.02%)	1 / 129 (0.78%)
occurrences (all)	0	14	1
CONSTIPATION			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	7 / 129 (5.43%)
occurrences (all)	0	1	7
CROHN'S DISEASE			
subjects affected / exposed	4 / 69 (5.80%)	13 / 171 (7.60%)	5 / 129 (3.88%)
occurrences (all)	4	13	5
NAUSEA			
subjects affected / exposed	1 / 69 (1.45%)	8 / 171 (4.68%)	3 / 129 (2.33%)
occurrences (all)	1	9	3
VOMITING			
subjects affected / exposed	0 / 69 (0.00%)	4 / 171 (2.34%)	0 / 129 (0.00%)
occurrences (all)	0	5	0
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	0 / 69 (0.00%)	4 / 171 (2.34%)	18 / 129 (13.95%)
occurrences (all)	0	4	18
ALOPECIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	0 / 69 (0.00%)	2 / 171 (1.17%)	1 / 129 (0.78%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 69 (1.45%)	11 / 171 (6.43%)	2 / 129 (1.55%)
occurrences (all)	1	11	2
BACK PAIN			
subjects affected / exposed	1 / 69 (1.45%)	11 / 171 (6.43%)	0 / 129 (0.00%)
occurrences (all)	1	12	0

FISTULA DISCHARGE			
subjects affected / exposed	0 / 69 (0.00%)	0 / 171 (0.00%)	0 / 129 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
INFLUENZA			
subjects affected / exposed	3 / 69 (4.35%)	2 / 171 (1.17%)	1 / 129 (0.78%)
occurrences (all)	3	2	1
FOLLICULITIS			
subjects affected / exposed	0 / 69 (0.00%)	1 / 171 (0.58%)	2 / 129 (1.55%)
occurrences (all)	0	1	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 69 (2.90%)	5 / 171 (2.92%)	1 / 129 (0.78%)
occurrences (all)	2	5	1
NASOPHARYNGITIS			
subjects affected / exposed	2 / 69 (2.90%)	5 / 171 (2.92%)	2 / 129 (1.55%)
occurrences (all)	2	5	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2017	The following changes were implemented with Amendment 1: -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	The following changes were implemented with Amendment 2: -Added vedolizumab as a prohibited biologic therapy during the study. -Clarified that the primary variables would be analysed for subjects enroled in Part 1. -Clarified that the secondary variables would be analysed for subjects enroled in Part 1. -Added SES-CD ≤ 2 at Week 12 to be consistent with pre-specified endpoint analysis for descriptive statistics. -Clarification on the pre-specified endpoint analysis for descriptive statistics for subjects enroled in Part 2. -Added pre-specified endpoints for descriptive statistics for subjects enroled in Part 3. -Clarification on the analysis methods considered for continuous secondary endpoints.
24 August 2018	The following changes were implemented with Amendment 3: -Updated the introduction to add 52-week data from AbbVie Study M13-740 (NCT02365649) and to clarify that the once-daily modified release formulation is being used in this study. -Updated overall study design and plan to note that the minimum Screening Period duration was corrected to reflect the minimum number of days for abdominal pain and stool frequency, accounting for the exclusion of non-usable days due to endoscopy-related procedures. -Updated eligibility criteria. -Clarified and provided additional guidance on the use of corticosteroids during the study. -Corrected the cutoff age for females in defining postmenopausal and updated contraception language. -Added the Montreal classification for Crohn's disease at Screening for the assessment of disease severity.
08 April 2019	The following changes were implemented with Amendment 4: -Updated overall study design and plan. -Updated exclusion criteria to ensure more appropriate selection of subjects into the study to avoid interference with efficacy assessments, to minimize or better manage the potential risks to the participants, and/or to provide further clarifications. -Removed mention of Japan and China from text describing conditions under which a chest x-ray will not be required, as a prior computerized tomography (CT) scan can apply to subjects from any country. -Updated toxicity management to align with the entire upadacitinib clinical programs, based on cumulative data with the compound. -Updated secondary efficacy variables to ensure accurate descriptions of statistical methods.
29 April 2020	The following changes were implemented with Amendment 5: -Updated introduction to include results of recent long-term integrated data from the Phase 3 Rheumatoid Arthritis program and the recent risk updates to the Janus kinase (JAK) inhibitor class. -Updated overall study design. -Updated eligibility criteria. -Updated efficacy variables: Changed co-primary efficacy endpoint to clinical remission based on CDAI for the United States Food and Drug Administration (US/FDA). -The European Union/European Medicines Agency (EU/EMA) co-primary efficacy endpoint for clinical remission remained based on PROs. -Ranked secondary variables then included change from Baseline in IBDQ at Week 12, proportion of subjects achieving CR-100 at Week 2 and Week 12, and assessment of extraintestinal manifestations. -Four variables (proportion of subjects with enhanced clinical response, ≥50% reduction in draining fistulas, response in IBDQ bowel domain at Week 12 and change from baseline in CSS) were not to be ranked but included under additional efficacy variables. -Updated toxicity management section. -Added management of missing date due to COVID-19.

24 September 2020	The following changes were implemented with Amendment 6: - 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.
05 March 2021	The following changes were implemented with Amendment 7: -Updated protocol to decrease the sample size of Part 2 from approximately 150 subjects to approximately 130 subjects, and consequently the total sample size from 645 to 625 subjects. -Increased the maximum percentage of subjects enroled who have had inadequate response or intolerance to 3 or more biologics from 30% to 35%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported