Clinical trial results:
A Phase 2 Study, Multicenter, Open-Label Extension (OLE) Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial (RCT) with Upadacitinib (ABT-494)

Summary

EudraCT number	2013-003530-33
Trial protocol	ES HU CZ GB NL LV BE BG
Global end of trial date	29 July 2021

Results information

Result version number	v1 (current)
This version publication date	27 July 2022
First version publication date	27 July 2022

Trial information

Trial identification

Sponsor protocol code	M13-538

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02049138
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
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	29 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the long-term safety, tolerability, and efficacy of upadacitinib in rheumatoid arthritis (RA) subjects who have completed Study M13-550 (2013-002358-57) or Study M13-537 (2013-003984-72) Phase 2 randomized clinical trial (RCT) with upadacitinib.

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	24 January 2014
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	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Chile: 28
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 48
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Puerto Rico: 12
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 166
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	493
EEA total number of subjects	229

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)	367
From 65 to 84 years	124
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants must have completed a preceding rheumatoid arthritis upadacitinib randomized controlled trial, Study M13-550 (2013-002358-57)) or Study M13-537 (2013-003984-72) to be enrolled in this long-term extension study.
Participants were enrolled at 113 study sites located in 17 countries.

Pre-assignment

Screening details:

Participants were assigned to upadacitinib 6 mg twice-daily up to 30 days following the Last Visit (Week 12) of the preceding RCT. Participants may have been up-titrated to 12 mg BID and subsequently down-titrated per protocol-specified criteria. Participants may have enrolled in a vaccine substudy during the main study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Upadacitinib Never Titrated

Arm description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg twice a day (BID). From January 2017 participants were transitioned to once-daily (QD) dose of 15 mg upadacitinib and remained on this dose throughout the study.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

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:

Tablets taken by mouth

Investigational medicinal product name	Pneumococcal 13-valent conjugate vaccine (PCV-13)
Investigational medicinal product code	
Other name	Prevnar 13®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administered by intramuscular injection

Arm title	Upadacitinib Titrated Up and Not Down

Arm description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib and remained on this dose throughout the study.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

Arm type	Active comparator

Investigational medicinal product name	Pneumococcal 13-valent conjugate vaccine (PCV-13)
Investigational medicinal product code	
Other name	Prevnar 13®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administered by intramuscular injection

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:

Tablets taken by mouth

Arm title	Upadacitinib Titrated Up and Down

Arm description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib. The upadacitinib dose was decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment or safety and/or tolerability concerns.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

Arm type	Experimental
Investigational medicinal product name	Pneumococcal 13-valent conjugate vaccine (PCV-13)
Investigational medicinal product code	
Other name	Prevnar 13®
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administered by intramuscular injection

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:

Tablets taken by mouth

Number of subjects in period 1	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down
Started	306	149	38
Enrolled in Vaccine Sub-study	76 [1]	24 [2]	11 [3]
Completed	142	51	30
Not completed	164	98	8
Required Alternative / Prohibited Therapy	1	1	-
Consent withdrawn by subject	57	21	5
Non-Compliance	15	6	-

Adverse event, non-fatal	46	25	1
COVID-19 Logistical Restrictions	1	-	-
Other	15	13	-
Coronavirus Disease-2019 (COVID-19) Infection	1	-	-
Lost to follow-up	18	5	1
Missing	-	1	-
Lack of efficacy	10	26	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A subset of participants were enrolled in the vaccine sub-study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A subset of participants were enrolled in the vaccine sub-study

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A subset of participants were enrolled in the vaccine sub-study

Baseline characteristics

Reporting groups	
Reporting group title	Upadacitinib Never Titrated
Reporting group description:	
Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg twice a day (BID). From January 2017 participants were transitioned to once-daily (QD) dose of 15 mg upadacitinib and remained on this dose throughout the study. A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).	
Reporting group title	Upadacitinib Titrated Up and Not Down
Reporting group description:	
Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib and remained on this dose throughout the study. A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).	
Reporting group title	Upadacitinib Titrated Up and Down
Reporting group description:	
Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib. The upadacitinib dose was decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment or safety and/or tolerability concerns. A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).	

Reporting group values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down
Number of subjects	306	149	38
Age categorical Units: Subjects			
< 45 years	56	30	5
45 - < 65 years	174	76	28
≥ 65 years	76	43	5
Age continuous Units: years			
arithmetic mean	55.8	56.0	53.7
standard deviation	± 12.62	± 12.56	± 8.54
Gender categorical Units: Subjects			
Female	246	117	29
Male	60	32	9
Race Units: Subjects			
White	293	132	37
Black or African American	9	12	1
Asian	1	2	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1	0	0
Multiple	2	3	0
Ethnicity			

Units: Subjects			
Hispanic or Latino	76	40	7
Not Hispanic or Latino	230	109	31
Region Units: Subjects			
Western Europe	27	13	5
Eastern Europe	144	46	19
North America	90	78	10
South/Central America	42	5	3
Other	3	7	1
Duration of RA Units: years			
arithmetic mean	9.34	9.61	7.66
standard deviation	± 8.73	± 8.36	± 6.54
Tender Joint Count			
A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: joints			
arithmetic mean	25.8	30.4	31.3
standard deviation	± 14.49	± 15.90	± 15.67
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: joints			
arithmetic mean	16.7	18.8	19.3
standard deviation	± 10.45	± 12.03	± 9.53
Physician's Global Assessment of Disease Activity			
The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a visual analog scale (VAS) from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. The number of participants with available data in each treatment group was 298, 147, and 38, respectively.			
Units: score on a scale			
arithmetic mean	64.4	65.6	65.0
standard deviation	± 15.82	± 15.41	± 15.41
Patient's Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. The number of participants with available data in each treatment group was 305, 146, and 37, respectively.			
Units: score on a scale			
arithmetic mean	62.4	67.4	66.5
standard deviation	± 20.78	± 20.52	± 16.48
Patient's Global Assessment of Pain			
Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." The number of participants with available data in each treatment group was 305, 146, and 37, respectively.			
Units: score on a scale			
arithmetic mean	63.8	67.2	66.5
standard deviation	± 19.73	± 19.64	± 13.13
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
The HAQ-DI is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping,			

and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). The overall score ranges from 0 to 3, where 0 represents no disability and 3 represents very severe, high-dependency disability. Participants with available data in each treatment group was 304, 146, and 37, respectively			
Units: score on a scale			
arithmetic mean	1.4811	1.6036	1.5304
standard deviation	± 1.6848	± 0.6215	± 0.4969
High-sensitivity reactive Protein (hsCRP)			
The number of participants with available data in each treatment group was 306, 149, and 38, respectively.			
Units: mg/L			
arithmetic mean	12.8968	14.9212	17.1232
standard deviation	± 17.8329	± 20.1890	± 28.1184

Reporting group values	Total		
Number of subjects	493		
Age categorical Units: Subjects			
< 45 years	91		
45 - < 65 years	278		
≥ 65 years	124		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	392		
Male	101		
Race Units: Subjects			
White	462		
Black or African American	22		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	1		
Multiple	5		
Ethnicity Units: Subjects			
Hispanic or Latino	123		
Not Hispanic or Latino	370		
Region Units: Subjects			
Western Europe	45		
Eastern Europe	209		
North America	178		
South/Central America	50		
Other	11		
Duration of RA Units: years arithmetic mean standard deviation	- -		

Tender Joint Count			
A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: joints arithmetic mean standard deviation	- 		
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: joints arithmetic mean standard deviation	- 		
Physician's Global Assessment of Disease Activity			
The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a visual analog scale (VAS) from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. The number of participants with available data in each treatment group was 298, 147, and 38, respectively.			
Units: score on a scale arithmetic mean standard deviation	- 		
Patient's Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. The number of participants with available data in each treatment group was 305, 146, and 37, respectively.			
Units: score on a scale arithmetic mean standard deviation	- 		
Patient's Global Assessment of Pain			
Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." The number of participants with available data in each treatment group was 305, 146, and 37, respectively.			
Units: score on a scale arithmetic mean standard deviation	- 		
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
The HAQ-DI is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). The overall score ranges from 0 to 3, where 0 represents no disability and 3 represents very severe, high-dependency disability. Participants with available data in each treatment group was 304, 146, and 37, respectively			
Units: score on a scale arithmetic mean standard deviation	- 		
High-sensitivity reactive Protein (hsCRP)			
The number of participants with available data in each treatment group was 306, 149, and 38, respectively.			
Units: mg/L arithmetic mean standard deviation	- 		

End points reporting groups

Reporting group title	Upadacitinib Never Titrated

Reporting group description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg twice a day (BID). From January 2017 participants were transitioned to once-daily (QD) dose of 15 mg upadacitinib and remained on this dose throughout the study.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

Reporting group title	Upadacitinib Titrated Up and Not Down

Reporting group description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib and remained on this dose throughout the study.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

Reporting group title	Upadacitinib Titrated Up and Down

Reporting group description:

Participants received treatment with upadacitinib for up to 312 weeks. The starting dose was 6 mg BID. Participants who did not achieve protocol-specified improvement criteria at Week 6 or at any visits thereafter were up-titrated to upadacitinib 12 mg BID. From January 2017 participants were transitioned to once-daily dose of 30 mg upadacitinib. The upadacitinib dose was decreased back to 6 mg BID (or 15 mg QD from January 2017) per Investigator's judgment or safety and/or tolerability concerns.
A subset of participants who opted-in to the vaccine substudy received a single-dose of 0.5mL intramuscular injection of pneumococcal 13-valent conjugate vaccine (PCV-13).

Subject analysis set title	Upadacitinib 15 mg + PCV-13
Subject analysis set type	Full analysis

Subject analysis set description:

Participants receiving 15 mg upadacitinib QD were administered a single-dose of pneumococcal 13-valent conjugate vaccine (PCV-13).
The sub-study full analysis set (FAS) included all participants enrolled in the sub-study who received PCV-13 vaccination and at least 1 dose of upadacitinib after vaccination during the sub-study.

Subject analysis set title	Upadacitinib 30 mg + PCV-13
Subject analysis set type	Full analysis

Subject analysis set description:

Participants receiving 30 mg upadacitinib QD were administered a single-dose of pneumococcal 13-valent conjugate vaccine (PCV-13).
The sub-study FAS included all participants enrolled in the sub-study who received PCV-13 vaccination and at least 1 dose of upadacitinib after vaccination during the sub-study.

Primary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response Over Time

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response Over Time[1]

End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR20 response criteria:
1. ≥ 20% improvement in 68-tender joint count;
2. ≥ 20% improvement in 66-swollen joint count; and
3. ≥ 20% improvement in at least 3 of the 5 following parameters:
   - Physician global assessment of disease activity;
   - Patient global assessment of disease activity;
   - Patient assessment of pain;
   - Health Assessment Questionnaire - Disability Index (HAQ-DI);
   - High-sensitivity C-reactive protein (hsCRP).

End point type	Primary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

Notes:

[1] - 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 tests were conducted; only descriptive statistics and confidence intervals were provided.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[2]	149[3]	38[4]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 277, 143, 36)	87.7	73.4	77.8	
Week 12 (N = 273, 141, 37)	89.0	73.8	75.7	
Week 24 (N = 256, 131, 35)	91.8	73.3	88.6	
Week 36 (N = 246, 125, 35)	90.2	83.2	82.9	
Week 48 (N = 229, 117, 34)	90.0	82.1	88.2	
Week 60 (N = 217, 105, 35)	95.4	83.8	85.7	
Week 72 (N = 199, 101, 32)	93.0	84.2	90.6	
Week 84 (N = 203, 97, 32)	94.6	76.3	96.9	
Week 96 (N = 204, 93, 33)	92.2	86.0	90.9	
Week 108 (N = 194, 91, 33)	94.8	85.7	87.9	
Week 120 (N = 186, 86, 29)	96.2	89.5	96.6	
Week 132 (N = 181, 80, 30)	93.9	87.5	96.7	
Week 144 (N = 178, 75, 27)	94.9	88.0	88.9	
Week 156 (N = 176, 73, 27)	92.0	87.7	92.6	
Week 168 (N = 172, 71, 29)	91.9	88.7	82.8	
Week 180 (N = 179, 67, 29)	93.9	79.1	86.2	
Week 192 (N = 168, 70, 28)	93.5	87.1	92.9	
Week 204 (N = 166, 69, 29)	94.0	81.2	86.2	
Week 216 (N = 160, 64, 27)	92.5	85.9	85.2	
Week 228 (N = 149, 55, 28)	96.0	83.6	92.9	
Week 240 (N = 153, 61, 28)	92.8	85.2	89.3	
Week 252 (N = 149, 58, 30)	94.0	87.9	86.7	
Week 264 (N = 135, 54, 28)	93.3	81.5	89.3	
Week 276 (N = 128, 52, 27)	93.8	84.6	81.5	
Week 288 (N = 133, 50, 27)	94.7	88.0	88.9	
Week 300 (N = 125, 50, 23)	94.4	82.0	87.0	
Week 312 (N = 129, 49, 26)	92.2	87.8	88.5	

Notes:

[2] - Open-label treated population with available data at each time point

[3] - Open-label treated population with available data at each time point

[4] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response Over Time

End point title	Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response Over Time[5]

End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR50 response criteria:
1. ≥ 50% improvement in 68-tender joint count;
2. ≥ 50% improvement in 66-swollen joint count; and
3. ≥ 50% improvement in at least 3 of the 5 following parameters:
   - Physician global assessment of disease activity;
   - Patient global assessment of disease activity;
   - Patient assessment of pain;
   - Health Assessment Questionnaire - Disability Index (HAQ-DI);
   - High-sensitivity C-reactive protein (hsCRP).

End point type	Primary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

Notes:

[5] - 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 tests were conducted; only descriptive statistics and confidence intervals were provided.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[6]	149[7]	38[8]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 275, 144, 35)	63.6	37.5	48.6	
Week 12 (N = 275, 141, 35)	73.5	41.8	45.7	
Week 24 (N = 251, 131, 35)	75.7	49.6	60.0	
Week 36 (N = 145, 126, 34)	73.5	51.6	55.9	
Week 48 (N = 229, 116, 36)	72.5	50.0	55.6	
Week 60 (N = 213, 108, 35)	79.8	52.8	65.7	
Week 72 (N = 201, 102, 33)	77.1	49.0	63.6	
Week 84 (N = 203, 95, 33)	78.8	55.8	75.8	
Week 96 (N = 202, 93, 33)	74.8	53.8	63.6	
Week 108 (N = 194, 93, 34)	79.4	54.8	58.8	
Week 120 (N = 187, 88, 29)	80.7	58.0	72.4	
Week 132 (N = 178, 80, 29)	79.2	56.3	69.0	
Week 144 (N = 178, 73, 28)	76.4	65.8	60.7	
Week 156 (N = 176, 71, 26)	79.5	63.4	76.9	
Week 168 (N = 173, 72, 29)	79.2	61.1	75.9	
Week 180 (N = 178, 70, 29)	80.9	64.3	65.5	
Week 192 (N = 166, 69, 26)	80.7	59.4	76.9	
Week 204 (N = 163, 69, 29)	82.2	59.4	79.3	
Week 216 (N = 158, 63, 27)	76.6	55.6	66.7	
Week 228 (N = 149, 55, 28)	79.2	58.2	67.9	
Week 240 (N = 152, 61, 28)	79.6	63.9	71.4	
Week 252 (N = 148, 58, 30)	83.8	55.2	76.7	
Week 264 (N = 133, 55, 28)	79.7	60.0	75.0	
Week 276 (N = 129, 51, 27)	84.5	52.9	66.7	
Week 288 (N = 135, 51, 26)	82.2	58.8	61.5	

Week 300 (N = 127, 49, 23)	75.6	61.2	56.5	
Week 312 (N = 127, 49, 26)	84.3	69.4	69.2	

Notes:

[6] - Open-label treated population with available data at each time point

[7] - Open-label treated population with available data at each time point

[8] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response Over Time

End point title	Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response Over Time[9]

End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR70 response criteria:
1. ≥ 70% improvement in 68-tender joint count;
2. ≥ 70% improvement in 66-swollen joint count and;
3. ≥ 70% improvement in at least 3 of the 5 following parameters:
   - Physician global assessment of disease activity;
   - Patient global assessment of disease activity;
   - Patient assessment of pain;
   - Health Assessment Questionnaire - Disability Index (HAQ-DI);
   - High-sensitivity C-reactive protein (hsCRP).

End point type	Primary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

Notes:

[9] - 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 tests were conducted; only descriptive statistics and confidence intervals were provided.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[10]	149[11]	38[12]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 273, 146, 37)	38.8	15.1	21.6	
Week 12 (N = 274, 144, 37)	47.1	18.1	24.3	
Week 24 (N = 253, 134, 35)	45.5	27.6	37.1	
Week 36 (N = 243, 127, 35)	49.0	28.3	34.3	
Week 48 (N = 226, 116, 36)	57.1	26.7	25.0	
Week 60 (N = 211, 110, 35)	60.2	30.0	42.9	
Week 72 (N = 204, 103, 33)	56.4	29.1	36.4	
Week 84 (N = 204, 95, 33)	60.3	29.5	54.5	
Week 96 (N = 199, 94, 33)	57.3	34.0	42.4	
Week 108 (N = 192, 91, 34)	59.9	31.9	47.1	
Week 120 (N = 187, 88, 29)	59.4	30.7	62.1	
Week 132 (N = 178, 80, 29)	61.8	33.8	48.3	

Week 144 (N = 172, 73, 28)	57.6	34.2	39.3	
Week 156 (N = 173, 71, 27)	64.7	38.9	55.6	
Week 168 (N = 170, 71, 29)	62.9	42.3	58.6	
Week 180 (N = 176, 71, 29)	59.1	29.6	48.3	
Week 192 (N = 163, 69, 27)	62.0	31.9	48.1	
Week 204 (N = 163, 68, 29)	65.0	42.6	58.6	
Week 216 (N = 159, 62, 28)	59.1	41.9	46.4	
Week 228 (N = 150, 56, 28)	60.0	39.3	60.7	
Week 240 (N = 151, 62, 28)	66.2	38.7	46.4	
Week 252 (N = 143, 58, 28)	62.9	29.3	50.0	
Week 264 (N = 135, 54, 28)	58.5	37.0	57.1	
Week 276 (N = 127, 52, 25)	66.1	34.6	48.0	
Week 288 (N = 132, 52, 27)	65.9	44.2	44.4	
Week 300 (N = 125, 51, 23)	60.8	41.2	43.5	
Week 312 (N = 130, 48, 27)	63.1	39.6	55.6	

Notes:

[10] - Open-label treated population with available data at each time point

[11] - Open-label treated population with available data at each time point

[12] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Satisfactory Humoral Response to PCV-13 Four Weeks After Vaccination

End point title	Percentage of Participants With Satisfactory Humoral Response to PCV-13 Four Weeks After Vaccination[13]

End point description:

Satisfactory humoral response is defined as greater than or equal to 2-fold increase in antibody concentration from the vaccination Baseline in at least 6 out of the 12 pneumococcal antigens 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).

End point type	Primary

End point timeframe:

Vaccination Baseline (defined as the last non-missing observation on or before the date of receiving PCV-13 vaccination) and 4 weeks after vaccination

Notes:

[13] - 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 tests were conducted; only descriptive statistics and confidence intervals were provided.

End point values	Upadacitinib 15 mg + PCV-13	Upadacitinib 30 mg + PCV-13		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83[14]	23[15]		
Units: percentage of participants				
number (confidence interval 95%)	67.5 (57.4 to 77.5)	56.5 (36.3 to 76.8)		

Notes:

[14] - The sub-study full analysis set with available data at the Week 4 visit of the sub-study.

[15] - The sub-study full analysis set with available data at the Week 4 visit of the sub-study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on Disease Activity Score-28 (DAS28[CRP]) Over Time

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on Disease Activity Score-28 (DAS28[CRP]) Over Time

End point description:

The DAS28(CRP) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (measured on a VAS from 0-100 mm), and hsCRP (in mg/L). Scores on the DAS28(CRP) range from 0 to approximately 10, where higher scores indicate more disease activity.
LDA is defined as a DAS28(CRP) score ≤ 3.2.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[16]	149[17]	38[18]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 279, 146, 37)	70.3	43.2	43.2	
Week 12 (N = 272, 145, 37)	77.9	43.4	43.2	
Week 24 (n = 255, 134, 36)	82.4	48.5	52.8	
Week 36 (N = 246, 128, 36)	80.5	50.8	55.6	
Week 48 (N = 228, 118, 37)	86.8	54.2	56.8	
Week 60 (N = 218, 110, 36)	86.2	56.4	66.7	
Week 72 (N = 203, 104, 33)	84.7	51.0	69.7	
Week 84 (N = 207, 98, 34)	88.9	60.2	85.3	
Week 96 (N = 205, 97, 34)	82.4	64.9	79.4	
Week 108 (N = 195, 92, 34)	88.2	66.3	70.6	
Week 120 (N = 185, 87, 31)	85.9	69.0	77.4	
Week 132 (N = 167, 77, 31)	88.6	70.1	87.1	
Week 144 (N = 169, 70, 28)	85.2	68.6	82.1	
Week 156 (N = 166, 67, 29)	86.1	74.6	86.2	
Week 168 (N = 160, 69, 30)	90.0	78.3	80.0	
Week 180 (N = 178, 69, 30)	90.4	69.6	80.0	
Week 192 (N = 169, 72, 27)	89.3	75.0	96.3	
Week 204 (N = 166, 70, 30)	88.6	61.4	83.3	
Week 216 (N = 159, 64, 28)	89.9	70.3	82.1	
Week 228 (N = 151, 55, 29)	89.4	70.9	86.2	
Week 240 (N = 153, 62, 29)	89.5	75.8	86.2	
Week 252 (N = 145, 58, 31)	91.7	67.2	83.9	
Week 264 (N = 130, 53, 28)	86.2	67.9	82.1	
Week 276 (N = 121, 54, 25)	91.7	74.1	72.0	

Week 288 (N = 106, 46, 25)	90.6	71.7	76.0	
Week 300 (N = 101, 37, 20)	94.1	67.6	80.0	
Week 312 (N = 116, 48, 27)	84.5	68.8	70.4	

Notes:

[16] - Open-label treated population with available data at each time point

[17] - Open-label treated population with available data at each time point

[18] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on Disease Activity Score-28 (DAS28[CRP]) Over Time

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on Disease Activity Score-28 (DAS28[CRP]) Over Time

End point description:

The DAS28 (CRP) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (measured on a VAS from 0-100 mm), and hsCRP (in mg/L). Scores on the DAS28(CRP) range from 0 to approximately 10, where higher scores indicate more disease activity.
Clinical remission is defined as a DAS28(CRP) score < 2.6.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[19]	149[20]	38[21]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 279, 146, 37)	53.0	21.2	29.7	
Week 12 (N = 272, 145, 37)	56.6	25.5	27.0	
Week 24 (N = 255, 134, 36)	60.8	31.3	38.9	
Week 36 (N = 246, 128, 36)	65.0	35.2	50.0	
Week 48 (N = 228, 118, 37)	66.2	36.4	35.1	
Week 60 (N = 218, 110, 36)	72.9	38.2	50.0	
Week 72 (N = 203, 104, 33)	69.0	35.6	51.5	
Week 84 (N = 207, 98, 34)	72.0	36.7	52.9	
Week 96 (N = 205, 97, 34)	71.7	45.4	52.9	
Week 108 (N = 195, 92, 34)	74.4	42.4	47.1	
Week 120 (N = 185, 87, 31)	74.1	49.4	45.2	
Week 132 (N = 167, 77, 31)	73.7	40.3	61.3	
Week 144 (N = 169, 70, 28)	71.0	44.3	60.7	
Week 156 (N = 166, 67, 29)	74.7	50.7	65.5	
Week 168 (N = 160, 69, 30)	77.5	49.3	66.7	

Week 180 (N = 178, 69, 30)	75.3	44.9	56.7	
Week 192 (N = 169, 72, 27)	76.9	47.2	55.6	
Week 204 (N = 166, 70, 30)	77.1	47.1	76.7	
Week 216 (N = 159, 64, 28)	79.2	56.3	53.6	
Week 228 (N = 151, 55, 29)	80.8	49.1	69.0	
Week 240 (N = 153, 62, 29)	75.2	50.0	69.0	
Week 252 (N = 145, 58, 31)	80.7	44.8	58.1	
Week 264 (N = 130, 53, 28)	73.8	39.6	67.9	
Week 276 (N = 121, 54, 25)	76.9	50.0	52.0	
Week 288 (N = 106, 46, 25)	74.5	47.8	48.0	
Week 300 (N = 101, 37, 20)	75.2	43.2	55.0	
Week 312 (N = 116, 48, 27)	72.4	45.8	63.0	

Notes:

[19] - Open-label treated population with available data at each time point

[20] - Open-label treated population with available data at each time point

[21] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on Clinical Disease Activity Index (CDAI) Over Time

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on Clinical Disease Activity Index (CDAI) Over Time

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, and Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity.
LDA is defined as a CDAI score ≤ 10

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[22]	149[23]	38[24]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 274, 142, 37)	65.3	35.2	35.1	
Week 12 (N = 273, 141, 34)	71.1	39.7	32.4	
Week 24 (N = 254, 133, 35)	80.3	46.6	51.4	
Week 36 (N = 243, 126, 35)	77.8	44.4	57.1	
Week 48 (N = 230, 118, 36)	83.0	50.8	38.9	
Week 60 (N = 218, 107, 36)	85.8	58.9	63.9	
Week 72 (N = 200, 104, 33)	85.5	46.2	60.6	

Week 84 (N = 205, 97, 32)	84.4	52.6	75.0	
Week 96 (N = 198, 96, 33)	81.3	63.5	57.6	
Week 108 (N = 194, 86, 33)	85.1	67.4	54.5	
Week 120 (N = 188, 88, 31)	87.2	67.0	77.4	
Week 132 (N = 182, 80, 30)	87.4	72.5	76.7	
Week 144 (N = 181, 75, 28)	88.4	68.0	78.6	
Week 156 (N = 178, 71, 28)	88.8	73.2	71.4	
Week 168 (N = 173, 73, 30)	90.8	82.2	83.3	
Week 180 (N = 179, 69, 30)	88.3	73.9	76.7	
Week 192 (N = 168, 70, 29)	88.1	70.0	79.3	
Week 204 (N = 164, 70, 29)	89.0	71.4	82.8	
Wek 216 (N = 158, 64, 28)	88.6	70.3	78.6	
Week 228 (N = 149, 56, 29)	89.3	67.9	79.3	
Week 240 (N = 153, 62, 29)	87.6	72.6	75.9	
Week 252 (N = 146, 57, 31)	89.0	73.7	74.2	
Week 264 (N = 133, 54, 29)	83.5	63.0	75.9	
Week 276 (N = 129, 53, 28)	87.6	67.9	67.9	
Week 288 (N = 134, 51, 28)	90.3	74.5	75.0	
Week 300 (N = 127, 50, 24)	89.8	72.0	70.8	
Week 312 (N = 127, 47, 26)	86.6	70.2	73.1	

Notes:

[22] - Open-label treated population with available data at each time point

[23] - Open-label treated population with available data at each time point

[24] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on Clinical Disease Activity Index (CDAI) Over Time

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on Clinical Disease Activity Index (CDAI) Over Time

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, and Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity.
Clinical remission is defined as a CDAI score ≤ 2.8.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[25]	149[26]	38[27]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 274, 142, 37)	23.4	4.9	10.8	
Week 12 (N = 273, 141, 34)	26.4	6.4	8.8	
Week 24 (N = 254, 133, 35)	28.3	12.8	14.3	
Week 36 (N = 243, 126, 35)	32.5	9.5	17.1	
Week 48 (N = 230, 118, 36)	34.8	11.0	11.1	
Week 60 (N = 218, 107, 36)	43.1	13.1	22.2	
Week 72 (N = 200, 104, 33)	43.5	12.5	9.1	
Week 84 (N = 205, 97, 32)	43.4	12.4	18.8	
Week 96 (N = 198, 96, 33)	40.4	15.6	21.2	
Week 108 (N = 194, 86, 33)	44.8	16.3	18.2	
Week 120 (N = 188, 88, 31)	43.6	12.5	22.6	
Week 132 (N = 182, 80, 30)	46.7	18.8	33.3	
Week 144 (N = 181, 75, 28)	38.1	14.7	28.6	
Week 156 (N = 178, 71, 28)	47.2	14.1	32.1	
Week 168 (N = 173, 73, 30)	48.6	20.5	33.3	
Week 180 (N = 179, 69, 30)	48.0	15.9	20.0	
Week 192 (N = 168, 70, 29)	46.4	18.6	24.1	
Week 204 (N = 164, 70, 29)	51.2	20.0	34.5	
Week 216 (N = 158, 64, 28)	46.2	21.9	28.6	
Week 228 (N = 149, 56, 29)	44.3	25.0	31.0	
Week 240 (N = 153, 62, 29)	51.6	24.2	31.0	
Week 252 (N = 146, 57, 31)	52.7	19.3	22.6	
Week 264 (N = 133, 54, 29)	48.1	20.4	17.2	
Week 276 (N = 129, 53, 28)	53.5	24.5	28.6	
Week 288 (N = 134, 51, 28)	51.5	25.5	28.6	
Week 300 (N = 127, 50, 24)	51.2	22.0	29.2	
Week 312 (N = 127, 47, 26)	50.4	27.7	34.6	

Notes:

[25] - Open-label treated population with available data at each time point

[26] - Open-label treated population with available data at each time point

[27] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on Simplified Disease Activity Index (SDAI) Over Time

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on Simplified Disease Activity Index (SDAI) Over Time

End point description:

The simplified disease activity index (SDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm and hsCRP (mg/dL). The total SDAI score ranges from 0 to 86 with higher scores indicating higher disease activity.
LDA is defined as a SDAI score ≤ 11.0.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[28]	149[29]	38[30]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 273, 142, 37)	54.2	25.4	32.4	
Week 12 (N = 270, 141, 34)	61.1	33.3	23.5	
Week 24 (N = 253, 133, 35)	66.8	33.1	48.6	
Week 36 (N = 242, 126, 35)	67.8	34.9	48.6	
Week 48 (N = 228, 118, 36)	73.7	38.1	41.7	
Week 60 (N = 218, 107, 36)	72.9	41.1	61.1	
Week 72 (N = 200, 104, 33)	71.5	36.5	51.5	
Week 84 (N = 205, 97, 32)	74.6	40.2	62.5	
Week 96 (N = 198, 96, 33)	71.2	45.8	51.5	
Week 108 (N = 194, 86, 33)	75.8	51.2	54.5	
Week 120 (N = 185, 87, 31)	74.6	55.2	64.5	
Week 132 (N = 166, 76, 30)	77.7	43.4	66.7	
Week 144 (N = 167, 70, 28)	70.7	44.3	67.9	
Week 156 (N = 164, 65, 28)	75.0	58.5	64.3	
Week 168 (N = 157, 69, 30)	75.8	59.4	66.7	
Week 180 (N = 178, 68, 30)	78.7	55.9	53.3	
Week 192 (N = 168, 70, 27)	76.2	52.9	66.7	
Week 204 (N = 164, 70, 29)	71.3	52.9	79.3	
Week 216 (N = 157, 64, 28)	79.0	56.3	57.1	
Week 228 (N = 149, 55, 29)	77.2	56.4	69.0	
Week 240 (N = 153, 62, 29)	74.5	50.0	69.0	
Week 252 (N = 143, 57, 31)	79.0	52.6	61.3	
Week 264 (N = 128, 52, 28)	71.1	51.9	67.9	
Week 276 (N = 121, 53, 25)	78.5	56.6	56.0	
Week 288 (N = 106, 46, 25)	74.5	56.5	68.0	
Week 300 (N = 101, 36, 19)	78.2	50.0	63.2	
Week 312 (N = 111, 45, 26)	72.1	48.9	65.4	

Notes:

[28] - Open-label treated population with available data at each time point

[29] - Open-label treated population with available data at each time point

[30] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on Simplified Disease Activity Index (SDAI) Over Time

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on Simplified Disease Activity Index (SDAI) Over Time

End point description:

The simplified disease activity index (SDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm and hsCRP (mg/dL). The total SDAI score ranges from 0 to 86 with higher scores indicating higher disease activity.
Clinical remission is defined as a SDAI score ≤ 3.3.

End point type	Secondary

End point timeframe:

Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[31]	149[32]	38[33]	
Units: percentage of participants				
number (not applicable)				
Week 6 (N = 273, 142, 37)	15.0	4.2	2.7	
Week 12 (N = 270, 141, 34)	17.8	2.8	5.9	
Week 24 (N = 253, 133, 35)	18.2	6.0	11.4	
Week 36 (N = 242, 126, 35)	23.6	4.0	8.6	
Week 48 (N = 228, 118, 36)	25.9	7.6	8.3	
Week 60 (N = 218, 107, 36)	32.6	12.1	13.9	
Week 72 (N = 200 , 104, 33)	31.0	9.6	9.1	
Week 84 (N = 205, 97, 32)	32.2	8.2	12.5	
Week 96 (N = 198, 96, 33)	28.8	13.5	18.2	
Week 108 (N = 194, 86, 33)	31.4	10.5	12.1	
Week 120 (N = 185, 87, 31)	33.5	8.0	12.9	
Week 132 (N = 166, 76, 30)	33.1	10.5	20.0	
Week 144 (N = 167, 70, 28)	26.3	5.7	14.3	
Week 156 (N = 164, 65, 28)	33.5	7.7	28.6	
Week 168 (N = 157, 69, 30)	31.8	11.6	26.7	
Week 180 (N = 178, 68, 30)	33.1	10.3	13.3	
Week 192 (N = 168, 70, 27)	32.7	12.9	14.8	
Week 204 (N = 164, 70, 29)	37.2	11.4	24.1	
Week 216 (N = 157, 64, 28)	32.5	10.9	10.7	
Week 228 (N = 149, 55, 29)	30.9	16.4	24.1	
Week 240 (N = 153, 62, 29)	34.0	14.5	10.3	
Week 252 (N = 143, 57, 31)	39.9	12.3	16.1	
Week 264 (N = 128, 52, 28)	32.8	11.5	7.1	
Week 276 (N = 121, 53, 25)	35.5	17.0	20.0	
Week 288 (N = 106, 46, 25)	35.8	19.6	8.0	
Week 300 (N = 101, 36, 19)	34.7	16.7	26.3	
Week 312 (N = 111, 45, 26)	30.6	15.6	26.9	

Notes:

[31] - Open-label treated population with available data at each time point

[32] - Open-label treated population with available data at each time point

[33] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Score Based on CRP (DAS28[CRP]) Over Time

End point title	Change From Baseline in Disease Activity Score Based on CRP (DAS28[CRP]) Over Time

End point description:

The disease activity score-28-CRP (DAS28 [CRP]) assesses RA disease activity based on a continuous scale of combined measures of 28 tender joint counts (TJC28), 28 swollen joint counts (SJC28), C-reactive protein (CRP), and the patient global assessment of disease activity (measured on a visual analog scale from 0 to 100 mm). DAS28(CRP) scores range from 0 to approximately 10 where higher scores indicate more disease activity. A negative change from Baseline in DAS28 (CRP) indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305[34]	146[35]	37[36]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 278, 144, 36)	-2.9 (± 1.21)	-2.4 (± 1.28)	-2.5 (± 1.01)	
Week 12 (N = 271, 143, 36)	-3.1 (± 1.14)	-2.5 (± 1.27)	-2.5 (± 1.03)	
Week 24 (N = 254, 132, 35)	-3.2 (± 1.07)	-2.7 (± 1.36)	-2.7 (± 1.22)	
Week 36 (N = 245, 126, 35)	-3.2 (± 1.20)	-2.9 (± 1.11)	-3.0 (± 1.17)	
Week 48 (N = 227, 116, 36)	-3.4 (± 1.20)	-2.9 (± 1.20)	-2.8 (± 0.97)	
Week 60 (N = 217, 108, 35)	-3.5 (± 1.15)	-2.9 (± 1.07)	-3.1 (± 0.98)	
Week 72 (N = 202, 102, 32)	-3.5 (± 1.03)	-2.9 (± 1.24)	-3.1 (± 0.88)	
Week 84 (N = 206, 96, 33)	-3.5 (± 1.06)	-3.1 (± 1.21)	-3.3 (± 0.62)	
Week 96 (N = 204, 95, 33)	-3.4 (± 1.11)	-3.1 (± 1.24)	-3.2 (± 0.98)	
Week 108 (N = 195, 91, 33)	-3.5 (± 1.09)	-3.1 (± 1.24)	-3.1 (± 0.94)	
Week 120 (N = 185, 86, 30)	-3.5 (± 1.08)	-3.1 (± 1.29)	-3.2 (± 0.86)	
Week 132 (N = 167, 77, 30)	-3.5 (± 1.02)	-3.1 (± 1.23)	-3.3 (± 1.02)	
Week 144 (N = 169, 70, 27)	-3.4 (± 1.13)	-3.0 (± 1.18)	-3.4 (± 1.04)	
Week 156 (N = 166, 67, 28)	-3.5 (± 1.13)	-3.1 (± 1.11)	-3.6 (± 1.00)	
Week 168 (N = 160, 68, 29)	-3.6 (± 1.17)	-3.2 (± 1.23)	-3.6 (± 1.08)	
Week 180 (N = 178, 68, 29)	-3.6 (± 1.10)	-3.2 (± 1.24)	-3.5 (± 1.13)	
Week 192 (N = 169, 72, 26)	-3.6 (± 1.15)	-3.2 (± 1.31)	-3.6 (± 1.06)	
Week 204 (N = 166, 70, 29)	-3.6 (± 1.13)	-3.1 (± 1.32)	-3.7 (± 1.13)	

Week 216 (N = 159, 64, 27)	-3.6 (± 1.13)	-3.2 (± 1.15)	-3.5 (± 1.02)	
Week 228 (N = 151, 54, 28)	-3.6 (± 1.12)	-3.3 (± 1.37)	-3.7 (± 0.91)	
Week 240 (N = 153, 61, 28)	-3.7 (± 1.12)	-3.2 (± 1.30)	-3.5 (± 0.91)	
Week 252 (N = 145, 58, 30)	-3.7 (± 1.20)	-3.3 (± 1.18)	-3.3 (± 1.04)	
Week 264 (N = 130, 53, 27)	-3.5 (± 1.25)	3.1 (± 1.25)	-3.4 (± 1.01)	
Week 276 (N = 121, 53, 24)	-3.7 (± 1.01)	-3.1 (± 1.22)	-3.5 (± 0.90)	
Week 288 (N = 106, 45, 24)	-3.7 (± 1.08)	-3.3 (± 1.44)	-3.2 (± 0.75)	
Week 300 (N = 101, 36, 19)	-3.7 (± 1.00)	-3.0 (± 1.38)	-3.4 (± 0.81)	
Week 312 (N = 116, 47, 26)	-3.5 (± 1.10)	-3.2 (± 1.25)	-3.2 (± 1.04)	

Notes:

[34] - Open-label treated population with available data at Baseline and each time point

[35] - Open-label treated population with available data at Baseline and each time point

[36] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Disease Activity Index (CDAI) Over Time

End point title	Change From Baseline in Clinical Disease Activity Index (CDAI) Over Time

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, and Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity. A negative change from Baseline indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	297[37]	144[38]	37[39]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 265, 138, 36)	-30.0 (± 12.49)	-27.5 (± 13.54)	-27.2 (± 11.42)	
Week 12 (N = 265, 137, 33)	-31.6 (± 11.82)	-28.4 (± 13.87)	-27.9 (± 11.12)	
Week 24 (N = 246, 129, 34)	-32.6 (± 11.81)	-30.6 (± 13.59)	-29.6 (± 11.45)	
Week 36 (N = 236, 122, 34)	-32.2 (± 12.43)	-31.4 (± 12.67)	-29.6 (± 11.63)	
Week 48 (N = 222, 114, 35)	-34.0 (± 12.84)	-31.8 (± 13.35)	-29.1 (± 10.82)	

Week 60 (N = 210, 103, 35)	-34.7 (± 12.52)	-32.4 (± 12.18)	-32.2 (± 12.09)	
Week 72 (N = 192, 100, 32)	-34.3 (± 11.71)	-32.3 (± 13.33)	-31.8 (± 10.88)	
Week 84 (N = 197, 93, 31)	-34.9 (± 12.08)	-31.0 (± 13.36)	-33.5 (± 9.66)	
Week 96 (N = 191, 92, 32)	-33.4 (± 11.71)	-32.1 (± 12.37)	-31.3 (± 10.86)	
Week 108 (N = 187, 83, 32)	-34.5 (± 11.83)	-32.4 (± 12.79)	-32.3 (± 10.81)	
Week 120 (N = 181, 85, 30)	-34.8 (± 11.87)	-32.3 (± 12.94)	-34.0 (± 10.75)	
Week 132 (N = 175, 79, 29)	-35.0 (± 12.24)	-32.7 (± 12.39)	-34.5 (± 12.14)	
Week 144 (N = 174, 74, 27)	-35.0 (± 12.21)	-33.1 (± 12.67)	-36.2 (± 12.03)	
Week 156 (N = 171, 69, 27)	-35.6 (± 12.24)	-33.6 (± 12.25)	-36.1 (± 11.80)	
Week 168 (N = 166, 70, 29)	-36.2 (± 13.01)	-33.8 (± 12.97)	-37.6 (± 13.08)	
Week 180 (N = 172, 66, 29)	-35.5 (± 12.60)	-34.0 (± 12.13)	-36.9 (± 12.07)	
Week 192 (N = 161, 68, 28)	-35.6 (± 12.25)	-34.0 (± 12.89)	-38.6 (± 11.76)	
Week 204 (N = 157, 68, 28)	-36.0 (± 12.36)	-33.8 (± 13.69)	-37.9 (± 12.59)	
Week 216 (N = 151, 62, 27)	-35.8 (± 13.19)	-33.9 (± 11.87)	-37.3 (± 11.62)	
Week 228 (N = 143, 53, 28)	-35.6 (± 12.68)	-35.5 (± 13.31)	-37.9 (± 11.55)	
Week 240 (N = 146, 59, 28)	-36.4 (± 12.95)	-34.7 (± 3.02)	-35.8 (± 11.07)	
Week 252 (N = 139, 55, 30)	-35.9 (± 13.41)	-35.3 (± 12.58)	-34.3 (± 11.71)	
Week 264 (N = 126, 52, 28)	-35.5 (± 13.66)	-33.2 (± 12.38)	-33.5 (± 12.49)	
Week 276 (N = 122, 50, 27)	-36.5 (± 12.59)	-33.6 (± 12.16)	-34.7 (± 11.92)	
Week 288 (N = 129, 48, 27)	-36.9 (± 13.22)	-35.3 (± 14.34)	-33.5 (± 10.25)	
Week 300 (N = 120, 47, 23)	-36.0 (± 12.17)	-32.9 (± 11.86)	-34.6 (± 11.27)	
Week 312 (N = 120, 44, 25)	-35.9 (± 12.43)	-34.4 (± 12.63)	-34.0 (± 11.62)	

Notes:

[37] - Open-label treated population with available data at Baseline and each time point

[38] - Open-label treated population with available data at Baseline and each time point

[39] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SimplifiedDisease Activity Index (SDAI) Over Time

End point title	Change From Baseline in SimplifiedDisease Activity Index (SDAI) Over Time

End point description:

The simplified disease activity index (SDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count

(out of 28 evaluated joints), Patient's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm, Physician's Global Assessment of Disease Activity measured on a VAS from 0 to 10 cm and hsCRP (mg/dL). The total SDAI score ranges from 0 to 86 with higher scores indicating higher disease activity. A negative change from Baseline indicates improvement in disease activity.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	297[40]	144[41]	37[42]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 264, 138, 36)	-38.8 (± 25.57)	-37.2 (± 27.36)	-40.8 (± 29.76)	
Week 12 (N = 262, 137, 33)	-40.6 (± 24.84)	-38.6 (± 26.09)	-41.7 (± 30.24)	
Week 24 (N = 245, 129, 34)	-42.0 (± 23.35)	-36.7 (± 43.09)	-38.2 (± 33.62)	
Week 36 (N = 235, 122, 34)	-41.8 (± 25.10)	-41.6 (± 25.59)	-44.5 (± 31.98)	
Week 48 (N = 220, 114, 35)	-42.9 (± 23.24)	-41.6 (± 25.26)	-44.6 (± 29.09)	
Week 60 (N = 210, 103, 35)	-44.3 (± 24.21)	-42.5 (± 24.51)	-41.4 (± 22.38)	
Week 72 (N = 192, 100, 32)	-43.4 (± 24.62)	-41.9 (± 27.31)	-41.8 (± 21.19)	
Week 84 (N = 197, 93, 31)	-42.7 (± 28.14)	-39.0 (± 31.94)	-44.7 (± 20.79)	
Week 96 (N = 191, 92, 32)	-42.0 (± 18.50)	-42.4 (± 27.17)	-43.2 (± 22.39)	
Week 108 (N = 187, 83, 32)	-43.6 (± 27.35)	-42.9 (± 24.31)	-44.0 (± 21.38)	
Week 120 (N = 178, 84, 30)	-42.7 (± 22.25)	-43.7 (± 25.88)	-43.4 (± 23.39)	
Week 132 (N = 165, 76, 29)	-43.4 (± 19.92)	-41.4 (± 27.64)	-44.2 (± 23.86)	
Week 144 (N = 166, 70, 27)	-41.7 (± 22.60)	-43.0 (± 29.91)	-46.0 (± 25.20)	
Week 156 (N = 163, 64, 27)	-42.8 (± 21.64)	-43.6 (± 29.88)	-48.0 (± 23.98)	
Week 168 (N = 156, 67, 29)	-43.7 (± 23.75)	-43.2 (± 28.55)	-46.4 (± 23.28)	
Week 180 (N = 171, 65, 29)	-45.6 (± 26.65)	-45.0 (± 27.57)	-47.2 (± 24.08)	
Week 192 (N = 161, 68, 26)	-44.7 (± 30.13)	-44.4 (± 27.94)	-48.5 (± 25.36)	
Week 204 (N = 157, 68, 28)	-44.1 (± 35.23)	-43.5 (± 28.81)	-47.6 (± 24.55)	
Week 216 (N = 150, 62, 27)	-47.3 (± 27.43)	-44.2 (± 26.69)	-47.4 (± 23.26)	
Week 228 (N = 143, 52, 28)	-46.0 (± 27.33)	-47.9 (± 28.86)	-48.6 (± 21.47)	
Week 240 (N = 146, 59, 28)	-46.8 (± 31.40)	-44.2 (± 29.63)	-45.0 (± 21.97)	

Week 252 (N = 136, 55, 30)	-45.9 (± 25.86)	-45.7 (± 29.98)	-44.3 (± 23.50)	
Week 264 (N = 121, 50, 27)	-44.9 (± 24.26)	-43.5 (± 30.06)	-44.4 (± 21.96)	
Week 276 (N = 114, 50, 24)	-46.3 (± 20.01)	-44.2 (± 26.93)	-47.4 (± 20.53)	
Week 288 (N = 105, 44, 24)	-47.1 (± 22.36)	-48.3 (± 30.14)	-41.6 (± 17.15)	
Week 300 (N = 98, 34, 18)	-47.4 (± 20.47)	-41.6 (± 26.38)	-42.7 (± 19.05)	
Week 312 (N = 110, 43, 25)	-45.8 (± 28.64)	-45.8 (± 28.89)	-41.2 (± 17.55)	

Notes:

[40] - Open-label treated population with available data at Baseline and each time point

[41] - Open-label treated population with available data at Baseline and each time point

[42] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tender Joint Count (TJC68) Over Time

End point title	Change From Baseline in Tender Joint Count (TJC68) Over Time

End point description:

Sixty-eight joints were assessed by an evaluator for tenderness or pain. The presence of tenderness was scored as a "1" and absence of tenderness as a "0". The total tender joint count is the sum of the scores, and ranges from 0 to 68 (worst).

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[43]	149[44]	38[45]	
Units: joints				
arithmetic mean (standard deviation)				
Week 6 (N = 284, 146, 37)	-20.6 (± 12.81)	-21.3 (± 14.53)	-22.1 (± 12.90)	
Week 12 (N = 280, 145, 37)	-21.3 (± 12.47)	-22.5 (± 14.65)	-20.5 (± 11.18)	
Week 24 (N = 258, 137, 36)	-22.0 (± 12.96)	-23.9 (± 14.60)	-22.9 (± 12.17)	
Week 36 (N = 248, 133, 36)	-21.7 (± 12.58)	-24.2 (± 14.45)	-23.4 (± 13.56)	
Week 48 (N = 234, 121, 37)	-23.1 (± 13.61)	-24.1 (± 14.43)	-24.0 (± 13.13)	
Week 60 (N = 218, 110, 36)	-23.6 (± 13.56)	-25.0 (± 14.42)	-25.6 (± 13.54)	
Week 72 (N = 204, 104, 33)	-23.3 (± 13.06)	-24.3 (± 14.48)	-26.1 (± 13.12)	

Week 84 (N = 209, 98, 34)	-23.2 (± 12.71)	-23.4 (± 14.23)	-27.4 (± 13.32)	
Week 96 (N = 206, 97, 34)	-23.1 (± 12.90)	-23.9 (± 14.58)	-24.6 (± 11.94)	
Week 108 (N = 195, 92, 34)	-23.3 (± 12.62)	-23.7 (± 14.22)	-25.2 (± 12.31)	
Week 120 (N = 189, 89, 31)	-23.1 (± 13.13)	-23.9 (± 14.17)	-26.9 (± 12.72)	
Week 132 (N = 184, 82, 31)	-23.1 (± 12.79)	-23.7 (± 13.95)	-26.8 (± 13.74)	
Week 144 (N = 183, 75, 28)	-23.5 (± 13.28)	-23.8 (± 13.50)	-29.3 (± 13.19)	
Week 156 (N = 181, 73, 30)	-23.7 (± 13.21)	-23.9 (± 13.00)	-28.1 (± 13.63)	
Week 168 (N = 177, 74, 30)	-24.1 (± 13.82)	-24.4 (± 13.86)	-31.0 (± 14.12)	
Week 180 (N = 180, 70, 30)	-23.7 (± 13.60)	-24.9 (± 14.12)	-29.5 (± 12.96)	
Week 192 (N = 169, 72, 29)	24.0 (± 13.75)	-24.4 (± 14.15)	-31.3 (± 13.80)	
Week 204 (N = 167, 70, 30)	-24.2 (± 13.77)	-23.6 (± 14.35)	-30.4 (± 14.53)	
Week 216 (N = 160, 64, 28)	24.2 (± 13.82)	-24.1 (± 13.87)	-31.6 (± 13.80)	
Week 228 (N = 154, 56, 30)	-23.9 (± 13.57)	-26.6 (± 14.65)	-30.5 (± 13.69)	
Week 240 (N = 154, 62, 29)	-24.7 (± 14.09)	-25.6 (± 14.47)	-29.4 (± 14.28)	
Week 252 (N = 148, 58, 31)	-24.2 (± 13.78)	-25.6 (± 14.14)	-27.5 (± 13.26)	
Week 264 (N = 135, 55, 29)	-23.7 (± 13.56)	-23.7 (± 13.28)	-27.0 (± 13.76)	
Week 276 (N = 129, 54, 28)	-23.6 (± 13.55)	-23.9 (± 13.76)	-28.0 (± 14.41)	
Week 288 (N = 137, 51, 28)	-24.9 (± 14.42)	-25.7 (± 14.87)	-26.6 (± 14.42)	
Week 300 (N = 127, 51, 26)	-24.3 (± 14.04)	-24.5 (± 15.18)	-28.2 (± 14.10)	
Weel 312 (N = 133, 50, 27)	-24.1 (± 13.82)	-23.2 (± 14.08)	-26.8 (± 14.48)	

Notes:

[43] - Open-label treated population with available data at each time point

[44] - Open-label treated population with available data at each time point

[45] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swollen Joint Count (SJC66) Over Time

End point title	Change From Baseline in Swollen Joint Count (SJC66) Over Time

End point description:

Sixty-six joints were assessed by an evaluator for swelling. The presence of swelling was scored as a "1" and absence of swelling as a "0". The total swollen joint count is the sum of the scores, and ranges from 0 to 66 (worst).

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144,

156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[46]	149[47]	38[48]	
Units: joints				
arithmetic mean (standard deviation)				
Week 6 (N = 284, 146, 37)	-12.8 (± 7.76)	-13.5 (± 10.89)	-14.5 (± 8.70)	
Week 12 (N = 280, 145, 37)	-13.7 (± 7.95)	-13.9 (± 11.26)	-13.5 (± 6.72)	
Week 24 (N = 258, 137, 36)	-14.2 (± 8.31)	-14.7 (± 10.87)	-15.7 (± 5.67)	
Week 36 (N = 248, 133, 36)	-14.1 (± 8.26)	-15.1 (± 10.39)	-15.6 (± 5.94)	
Week 48 (N = 234, 121, 37)	-15.3 (± 9.47)	-15.4 (± 11.19)	-16.0 (± 6.10)	
Week 60 (N = 218, 110, 36)	-15.6 (± 9.52)	-15.9 (± 11.83)	-17.4 (± 9.36)	
Week 72 (N = 204, 104, 33)	-15.1 (± 8.50)	-15.5 (± 10.47)	-17.0 (± 6.31)	
Week 84 (N = 209, 98, 34)	-15.6 (± 9.18)	-14.7 (± 9.96)	-17.0 (± 6.68)	
Week 96 (N = 206, 97, 34)	-15.3 (± 9.27)	-14.7 (± 9.48)	-16.6 (± 6.79)	
Week 108 (N = 195, 92, 34)	-15.2 (± 8.72)	-15.2 (± 10.17)	-16.6 (± 6.96)	
Week 120 (N = 189, 89, 31)	-15.6 (± 8.77)	-14.8 (± 9.06)	-17.5 (± 7.15)	
Week 132 (N = 184, 82, 31)	-15.7 (± 9.23)	-14.6 (± 9.79)	-17.3 (± 7.11)	
Week 144 (N = 183, 75, 28)	-15.9 (± 9.03)	-15.3 (± 9.81)	-18.6 (± 7.17)	
Week 156 (N = 181, 73, 30)	-16.1 (± 9.74)	-15.5 (± 9.53)	-17.5 (± 7.89)	
Week 168 (N = 177, 74, 30)	-16.9 (± 11.11)	-15.8 (± 10.51)	-20.0 (± 9.94)	
Week 180 (N = 180, 70, 30)	-16.6 (± 10.67)	-16.2 (± 10.61)	-20.0 (± 9.91)	
Week 192 (N = 169, 72, 29)	-16.4 (± 9.87)	-15.8 (± 9.23)	-20.7 (± 10.08)	
Week 204 (N = 167, 70, 30)	-16.7 (± 10.60)	-15.9 (± 9.53)	-19.6 (± 10.22)	
Week 216 (N = 160, 64, 28)	-16.6 (± 10.29)	-16.1 (± 8.86)	-20.4 (± 10.12)	
Week 228 (N = 154, 56, 30)	-16.2 (± 9.51)	-17.3 (± 10.79)	-19.8 (± 10.16)	
Week 240 (N = 154, 62, 29)	-16.8 (± 10.41)	-17.0 (± 10.43)	-18.8 (± 7.86)	
Week 252 (N = 148, 58, 31)	-16.8 (± 10.63)	-16.9 (± 9.37)	-18.1 (± 7.78)	
Week 264 (N = 135, 55, 29)	-17.7 (± 11.38)	-16.1 (± 8.72)	-18.3 (± 7.55)	
Week 276 (N = 129, 54, 28)	-17.8 (± 11.35)	-17.0 (± 10.60)	-18.9 (± 7.74)	
Week 288 (N = 137, 51, 28)	-17.4 (± 11.28)	-17.8 (± 11.76)	-18.7 (± 7.67)	
Week 300 (N = 127, 51, 26)	-16.7 (± 10.21)	-17.1 (± 10.31)	-19.3 (± 7.72)	

Week 312 (N = 133, 50, 27)	-16.7 (± 9.71)	-17.4 (± 10.41)	-18.6 (± 7.51)	

Notes:

[46] - Open-label treated population with available data at each time point

[47] - Open-label treated population with available data at each time point

[48] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician's Global Assessment of Disease Activity Over Time

End point title	Change From Baseline in Physician's Global Assessment of Disease Activity Over Time

End point description:

The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a visual analog scale (VAS) from 0 to 100 mm, where 0 mm indicates no disease activity and 100 mm indicates severe disease activity.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298[49]	147[50]	38[51]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 268, 140, 37)	-46.8 (± 20.58)	-35.5 (± 21.53)	-38.4 (± 24.08)	
Week 12 (N = 269, 140, 34)	-48.9 (± 20.45)	-39.1 (± 22.99)	-37.5 (± 21.78)	
Week 24 (N = 248, 133, 36)	-51.2 (± 18.71)	-42.5 (± 21.24)	-40.9 (± 22.79)	
Week 36 (N = 236, 124, 35)	-51.6 (± 19.08)	-42.7 (± 20.96)	-39.5 (± 24.20)	
Week 48 (N = 223, 116, 36)	-52.8 (± 19.12)	-45.6 (± 19.29)	-40.6 (± 20.97)	
Week 60 (N = 211, 106, 36)	-54.2 (± 16.44)	-47.1 (± 19.64)	-44.7 (± 24.33)	
Week 72 (N = 198, 103, 34)	-53.4 (± 17.46)	-45.9 (± 18.58)	-47.2 (± 18.47)	
Week 84 (N = 199, 96, 32)	-54.3 (± 16.44)	-43.4 (± 21.41)	-48.5 (± 17.25)	
Week 96 (N = 192, 95, 33)	-52.3 (± 17.69)	-45.7 (± 20.42)	-46.8 (± 20.97)	
Week 108 (N = 187, 86, 33)	-55.5 (± 16.72)	-45.9 (± 18.75)	-47.4 (± 21.09)	
Week 120 (N = 182, 86, 31)	-55.9 (± 16.38)	-48.6 (± 18.23)	-50.1 (± 21.51)	

Week 132 (N = 177, 79, 30)	-56.1 (± 16.60)	-50.1 (± 17.19)	-52.5 (± 20.62)	
Week 144 (N = 174, 74, 29)	-56.7 (± 15.79)	-48.2 (± 18.28)	-51.4 (± 19.66)	
Week 156 (N = 172, 70, 29)	-57.0 (± 16.90)	-48.9 (± 18.89)	-52.4 (± 19.49)	
Week 168 (N = 168, 73, 30)	-57.0 (± 15.94)	-51.9 (± 20.24)	-55.6 (± 21.25)	
Week 180 (N = 174, 68, 30)	-57.2 (± 17.11)	-53.0 (± 18.04)	-53.1 (± 19.34)	
Week 192 (N = 162, 68, 30)	-56.3 (± 17.25)	-52.1 (± 16.56)	-55.1 (± 20.69)	
Week 204 (N = 158, 69, 30)	-58.0 (± 16.73)	-52.9 (± 18.09)	-54.7 (± 19.50)	
Week 216 (N = 151, 63, 31)	-58.3 (± 16.50)	-50.8 (± 18.27)	-51.3 (± 20.42)	
Week 228 (N = 146, 55, 30)	-56.3 (± 19.63)	-53.2 (± 17.28)	-55.0 (± 19.69)	
Week 240 (N = 148, 61, 29)	-58.1 (± 17.63)	-52.8 (± 16.04)	-49.6 (± 18.67)	
Week 252 (N = 141, 55, 31)	-57.2 (± 17.56)	-53.9 (± 17.10)	-52.2 (± 18.12)	
Week 264 (N = 130, 52, 29)	-56.5 (± 16.68)	-50.4 (± 18.09)	-46.4 (± 18.60)	
Week 276 (N = 123, 52, 28)	-56.9 (± 16.79)	-53.5 (± 17.07)	-50.1 (± 17.96)	
Week 288 (N = 132, 51, 29)	-57.3 (± 18.97)	-56.3 (± 17.25)	-49.4 (± 16.31)	
Week 300 (N = 126, 50, 25)	-56.8 (± 17.93)	-52.9 (± 17.33)	-53.6 (± 17.36)	
Week 312 (N = 125, 45, 26)	-58.7 (± 16.12)	-55.2 (± 17.19)	-49.4 (± 17.96)	

Notes:

[49] - Open-label treated population with available data at Baseline and each time point

[50] - Open-label treated population with available data at Baseline and each time point

[51] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient's Global Assessment of Disease Activity Over Time

End point title	Change From Baseline in Patient's Global Assessment of Disease Activity Over Time

End point description:

The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305[52]	146[53]	37[54]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 280, 145, 36)	-35.4 (± 29.83)	-27.2 (± 27.74)	-26.1 (± 27.46)	
Week 12 (N = 275, 143, 36)	-37.5 (± 29.00)	-29.2 (± 28.05)	-31.3 (± 23.13)	
Week 24 (N = 257, 132, 36)	-36.9 (± 28.97)	-30.4 (± 31.16)	-32.9 (± 25.63)	
Week 36 (N = 246, 126, 35)	-37.1 (± 30.36)	-32.6 (± 28.62)	-34.9 (± 26.00)	
Week 48 (N = 229, 116, 36)	-39.2 (± 30.36)	-30.7 (± 30.46)	-23.6 (± 26.58)	
Week 60 (N = 219, 110, 35)	-40.8 (± 28.95)	-34.4 (± 28.36)	-38.3 (± 24.46)	
Week 72 (N = 208, 104, 33)	-40.3 (± 27.36)	-32.1 (± 30.19)	-26.3 (± 30.70)	
Week 84 (N = 209, 99, 33)	-40.1 (± 30.37)	-32.0 (± 31.27)	-39.4 (± 21.35)	
Week 96 (N = 205, 96, 33)	-38.1 (± 30.34)	-33.5 (± 33.51)	-33.5 (± 22.08)	
Week 108 (N = 195, 93, 33)	-40.8 (± 29.75)	-35.0 (± 29.93)	-32.1 (± 20.65)	
Week 120 (N = 188, 87, 30)	-40.6 (± 29.76)	-32.4 (± 32.91)	-36.6 (± 28.02)	
Week 132 (N = 184, 82, 30)	-40.1 (± 29.99)	-37.0 (± 28.43)	-38.4 (± 27.02)	
Week 144 (N = 183, 75, 28)	-37.7 (± 30.73)	-36.8 (± 28.24)	-33.9 (± 29.68)	
Week 156 (N = 180, 74, 28)	-39.7 (± 32.65)	-36.9 (± 25.93)	-38.6 (± 21.61)	
Week 168 (N = 177, 73, 29)	-42.7 (± 29.04)	-37.9 (± 29.10)	-39.0 (± 32.84)	
Week 180 (N = 179, 71, 29)	-40.3 (± 29.52)	-30.7 (± 33.34)	-33.3 (± 34.03)	
Week 192 (N = 170, 72, 30)	-41.0 (± 28.73)	-33.4 (± 33.30)	-42.1 (± 23.97)	
Week 204 (N = 166, 71, 30)	-42.0 (± 29.28)	-33.2 (± 34.00)	-43.7 (± 25.60)	
Week 216 (N = 161, 65, 30)	-39.0 (± 32.18)	-32.5 (± 30.72)	-35.6 (± 27.03)	
Week 228 (N = 153, 59, 30)	-38.4 (± 32.29)	-28.5 (± 37.86)	-40.1 (± 24.11)	
Week 240 (N = 155, 62, 28)	-41.9 (± 30.43)	-37.6 (± 28.56)	-33.3 (± 29.03)	
Week 252 (N = 151, 59, 30)	-40.6 (± 32.12)	-33.8 (± 31.76)	-33.5 (± 35.96)	
Week 264 (N = 140, 55, 28)	-38.5 (± 31.53)	-31.6 (± 34.26)	-32.7 (± 34.87)	
Week 276 (N = 130, 54, 27)	-42.4 (± 27.53)	-36.8 (± 29.40)	-26.0 (± 33.79)	
Week 288 (N = 138, 53, 28)	-43.3 (± 29.77)	-38.5 (± 32.21)	-32.2 (± 28.16)	
Week 300 (N = 134, 52, 27)	-38.8 (± 29.04)	-33.4 (± 34.89)	-31.6 (± 25.93)	
Week 312 (N = 137, 49, 27)	-36.5 (± 32.10)	-39.4 (± 30.60)	-37.7 (± 29.67)	

Notes:

[52] - Open-label treated population with available data at Baseline and each time point

[53] - Open-label treated population with available data at Baseline and each time point

[54] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient's Assessment of Pain Over Time

End point title	Change From Baseline in Patient's Assessment of Pain Over Time

End point description:

Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain."

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	305[55]	146[56]	37[57]	
Units: scpre on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 280, 145, 36)	-38.5 (± 27.16)	-29.9 (± 24.46)	-30.0 (± 26.37)	
Week 12 (N = 275, 143, 36)	-41.3 (± 26.07)	-29.9 (± 26.20)	-31.9 (± 20.23)	
Week 24 (N = 257, 132, 36)	-42.2 (± 25.41)	-30.9 (± 28.77)	-36.0 (± 21.73)	
Week 36 (N = 246, 126, 35)	-40.6 (± 26.41)	-34.6 (± 26.56)	-34.8 (± 21.83)	
Week 48 (N = 229, 116, 36)	-42.4 (± 26.50)	-31.9 (± 28.73)	-32.6 (± 23.67)	
Week 60 (N = 219, 110, 35)	-41.9 (± 27.89)	-32.2 (± 26.50)	-38.6 (± 23.34)	
Week 72 (N = 208, 104, 33)	-42.5 (± 24.76)	-32.0 (± 25.38)	-31.4 (± 22.95)	
Week 84 (N = 209, 99, 33)	-42.1 (± 25.87)	-33.3 (± 26.52)	-43.0 (± 20.51)	
Week 96 (N = 205, 96, 33)	-40.5 (± 28.02)	-34.2 (± 26.14)	-37.6 (± 20.15)	
Week 108 (N = 195, 93, 33)	-43.6 (± 26.28)	-33.9 (± 27.60)	-36.3 (± 23.12)	
Week 120 (N = 188, 87, 30)	-43.0 (± 26.67)	-36.2 (± 27.69)	-41.9 (± 21.40)	
Week 132 (N = 184, 82, 30)	-42.2 (± 26.89)	-36.7 (± 26.71)	-34.4 (± 27.27)	

Week 144 (N = 183, 75, 28)	-41.7 (± 27.02)	-36.7 (± 27.14)	-33.8 (± 24.60)	
Week 156 (N = 180, 74, 28)	-43.5 (± 25.72)	-37.4 (± 25.27)	-34.6 (± 24.91)	
Week 168 (N = 177, 73, 29)	-43.6 (± 27.19)	-38.8 (± 27.67)	-41.6 (± 25.76)	
Week 180 (N = 179, 71, 29)	-42.7 (± 26.54)	-33.6 (± 30.24)	-36.5 (± 29.20)	
Week 192 (N = 170, 72, 30)	-41.6 (± 27.90)	-33.8 (± 29.13)	-39.9 (± 25.44)	
Week 204 (N = 166, 71, 30)	-44.4 (± 25.26)	-33.4 (± 33.05)	-41.9 (± 22.39)	
Week 216 (N = 161, 65, 30)	-42.2 (± 28.01)	-32.5 (± 32.06)	-33.6 (± 25.98)	
Week 228 (N = 153, 59, 30)	-45.1 (± 24.96)	-29.6 (± 35.17)	-39.8 (± 24.70)	
Week 240 (N = 155, 62, 28)	-43.4 (± 27.78)	-34.1 (± 31.98)	-36.1 (± 25.38)	
Week 252 (N = 151, 59, 30)	-44.4 (± 27.49)	-34.3 (± 28.12)	-38.3 (± 24.92)	
Week 264 (N = 140, 55, 28)	-44.0 (± 25.43)	-35.6 (± 31.33)	-38.2 (± 24.11)	
Week 276 (N = 130, 54, 27)	-46.3 (± 24.53)	-35.6 (± 27.39)	-34.1 (± 26.80)	
Week 288 (N = 138, 53, 28)	-46.2 (± 25.61)	-37.6 (± 28.74)	-33.3 (± 23.30)	
Week 300 (N = 134, 52, 27)	-43.0 (± 25.18)	-34.7 (± 32.36)	-29.9 (± 30.21)	
Week 312 (N = 137, 49, 27)	-44.1 (± 25.87)	-40.3 (± 27.37)	-33.4 (± 30.11)	

Notes:

[55] - Open-label treated population with available data at Baseline and each time point

[56] - Open-label treated population with available data at Baseline and each time point

[57] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) Over Time

End point title	Change From Baseline in Health Assessment Questionnaire - Disability Index (HAQ-DI) Over Time

End point description:

The Health Assessment Questionnaire - Disability Index is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 to 3, where 0 represents no disability and 3 represents very severe, high-dependency disability.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304[58]	146[59]	37[60]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 264, 136, 35)	-0.7 (± 0.62)	-0.6 (± 0.56)	-0.6 (± 0.47)	
Week 12 (N = 264, 138, 34)	-0.7 (± 0.64)	-0.6 (± 0.63)	-0.7 (± 0.55)	
Week 24 (N = 236, 130, 33)	-0.8 (± 0.60)	-0.6 (± 0.61)	-0.7 (± 0.58)	
Week 36 (N = 235, 117, 32)	-0.7 (± 0.66)	-0.6 (± 0.62)	-0.7 (± 0.66)	
Week 48 (N = 213, 111, 34)	-0.8 (± 0.63)	-0.7 (± 0.61)	-0.7 (± 0.58)	
Week 60 (N = 206, 104, 34)	-0.8 (± 0.67)	-0.7 (± 0.66)	-0.7 (± 0.52)	
Week 72 (N = 194, 100, 33)	-0.8 (± 0.65)	-0.7 (± 0.63)	-0.7 (± 0.54)	
Week 84 (N = 196, 90, 32)	-0.9 (± 0.62)	-0.7 (± 0.64)	-0.7 (± 0.57)	
Week 96 (N = 192, 89, 30)	-0.8 (± 0.64)	-0.8 (± 0.69)	-0.8 (± 0.52)	
Week 108 (N = 185, 87, 33)	-0.9 (± 0.67)	-0.7 (± 0.67)	-0.7 (± 0.58)	
Week 120 (N = 178, 84, 29)	-0.8 (± 0.64)	-0.7 (± 0.64)	-0.8 (± 0.62)	
Week 132 (N = 176, 75, 28)	-0.9 (± 0.66)	-0.7 (± 0.64)	-0.8 (± 0.51)	
Week 144 (N = 170, 70, 27)	-0.8 (± 0.72)	-0.8 (± 0.68)	-0.7 (± 0.61)	
Week 156 (N = 172, 72, 26)	-0.8 (± 0.69)	-0.7 (± 0.57)	-0.8 (± 0.61)	
Week 168 (N = 168, 72, 27)	-0.8 (± 0.68)	-0.7 (± 0.67)	-0.8 (± 0.60)	
Week 180 (N = 169, 69, 28)	-0.8 (± 0.70)	-0.7 (± 0.70)	-0.7 (± 0.64)	
Week 192 (N = 160, 66, 26)	-0.8 (± 0.68)	-0.7 (± 0.69)	-0.8 (± 0.57)	
Week 204 (N = 160, 69, 28)	-0.9 (± 0.68)	-0.7 (± 0.79)	-0.8 (± 0.51)	
Week 216 (N = 155, 64, 30)	-0.8 (± 0.69)	-0.7 (± 0.73)	-0.8 (± 0.61)	
Week 228 (N = 146, 57, 29)	-0.9 (± 0.72)	-0.7 (± 0.77)	-0.7 (± 0.61)	
Week 240 (N = 146, 62, 28)	-0.8 (± 0.69)	-0.7 (± 0.77)	-0.6 (± 0.61)	
Week 252 (N = 139, 57, 27)	-0.9 (± 0.69)	-0.7 (± 0.77)	-0.7 (± 0.59)	
Week 264 (N = 136, 50, 27)	-0.8 (± 0.68)	-0.7 (± 0.65)	-0.7 (± 0.59)	
Week 276 (N = 127, 52, 27)	-0.8 (± 0.69)	-0.6 (± 0.66)	-0.7 (± 0.61)	
Week 288 (N = 125, 47, 26)	-0.9 (± 0.70)	-0.7 (± 0.74)	-0.8 (± 0.61)	
Week 300 (N = 128, 51, 24)	-0.8 (± 0.76)	-0.7 (± 0.70)	-0.7 (± 0.68)	
Week 312 (N = 129, 46, 27)	-0.8 (± 0.71)	-0.8 (± 0.74)	-0.7 (± 0.69)	

Notes:

[58] - Open-label treated population with available data at Baseline and each time point

[59] - Open-label treated population with available data at Baseline and each time point

[60] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in High-sensitivity C-reactive Protein (hsCRP) Over Time

End point title	Change From Baseline in High-sensitivity C-reactive Protein (hsCRP) Over Time

End point description:

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	306[61]	149[62]	38[63]	
Units: mg/L				
arithmetic mean (standard deviation)				
Week 6 (N = 297, 149, 38)	-7.9 (± 21.74)	-10.0 (± 21.95)	-13.0 (± 29.00)	
Week 12 (N = 282, 147, 38)	-9.0 (± 18.96)	-10.7 (± 20.94)	-12.8 (± 26.93)	
Week 24 (N = 264, 139, 38)	-9.4 (± 17.38)	-7.2 (± 36.97)	-9.1 (± 29.38)	
Week 36 (N = 254, 133, 38)	-9.5 (± 18.62)	-11.1 (± 22.03)	-13.5 (± 28.34)	
Week 48 (N = 239, 125, 38)	-8.8 (± 17.50)	-10.2 (± 22.28)	-13.3 (± 22.69)	
Week 60 (N = 227, 117, 37)	-9.6 (± 17.78)	-10.3 (± 22.10)	-11.0 (± 21.62)	
Week 72 (N = 222, 111, 36)	-9.2 (± 19.42)	-9.9 (± 22.95)	-11.2 (± 20.16)	
Week 84 (N = 217, 105, 35)	-8.3 (± 24.66)	-10.0 (± 28.56)	-10.2 (± 16.57)	
Week 96 (N = 213, 101, 35)	-10.1 (± 17.74)	-10.3 (± 22.36)	-11.1 (± 17.61)	
Week 108 (N = 206, 96, 35)	-9.8 (± 21.56)	-10.7 (± 19.36)	-10.8 (± 17.39)	
Week 120 (N = 198, 91, 32)	-8.4 (± 18.27)	-10.9 (± 19.63)	-9.2 (± 18.62)	
Week 132 (N = 181, 83, 33)	-8.9 (± 15.19)	-9.0 (± 21.32)	-9.3 (± 17.53)	
Week 144 (N = 180, 76, 32)	-7.3 (± 17.15)	-9.9 (± 23.45)	-5.9 (± 26.82)	
Week 156 (N = 176, 72, 32)	-8.6 (± 16.60)	-6.0 (± 52.17)	-10.9 (± 18.20)	
Week 168 (N = 171, 74, 32)	-7.7 (± 18.37)	-7.5 (± 28.96)	-8.8 (± 17.88)	
Week 180 (N = 185, 72, 32)	-10.0 (± 19.41)	-10.3 (± 21.44)	-9.2 (± 19.16)	
Week 192 (N = 177, 73, 30)	-9.4 (± 23.81)	-9.9 (± 21.04)	-9.3 (± 20.07)	
Week 204 (N = 174, 72, 32)	-8.4 (± 28.90)	-9.6 (± 21.29)	-9.0 (± 19.07)	
Week 216 (N = 166, 68, 32)	-11.5 (± 20.22)	-10.0 (± 22.42)	-8.4 (± 19.70)	
Week 228 (N = 165, 61, 31)	-11.0 (± 20.71)	-12.2 (± 20.89)	-10.0 (± 17.46)	
Week 240 (N = 163, 63, 32)	-10.6 (± 24.45)	-9.1 (± 22.38)	-9.2 (± 17.55)	
Week 252 (N = 151, 61, 31)	-10.4 (± 19.33)	-9.4 (± 24.28)	-9.9 (± 18.83)	
Week 264 (N = 141, 57, 28)	-11.2 (± 21.02)	-9.9 (± 23.99)	-11.1 (± 18.19)	
Week 276 (N = 135, 56, 27)	-10.5 (± 18.04)	-11.2 (± 20.20)	-10.9 (± 17.95)	
Week 288 (N = 115, 51, 26)	-10.6 (± 16.09)	-12.9 (± 21.85)	-7.5 (± 14.48)	
Week 300 (N = 113, 40, 22)	-11.1 (± 14.63)	-11.4 (± 21.67)	-11.0 (± 19.69)	
Week 312 (N = 124, 49, 29)	-10.3 (± 22.22)	-12.0 (± 21.14)	-8.7 (± 15.19)	

Notes:

[61] - Open-label treated population with available data at each time point

[62] - Open-label treated population with available data at each time point

[63] - Open-label treated population with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale Over Time

End point title	Change From Baseline in in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale Over Time

End point description:

The FACIT Fatigue scale is a 13-item tool that measures an individual's level of fatigue during their usual daily activities over the past 7 days. Each of the fatigue and impact of fatigue items are measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued). The FACIT Fatigue Scale is the sum of the individual 13 scores and ranges from 0 to 52 where higher scores indicate better quality of life. A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304[64]	146[65]	37[66]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 278, 145, 36)	9.5 (± 10.50)	9.0 (± 9.69)	8.8 (± 9.26)	
Week 12 (N = 275, 142, 36)	9.9 (± 10.49)	8.7 (± 10.87)	8.6 (± 10.43)	
Week 24 (N = 256, 133, 36)	10.7 (± 10.04)	10.6 (± 11.60)	8.3 (± 9.65)	
Week 36 (N = 244, 126, 35)	10.1 (± 10.59)	10.0 (± 11.58)	8.0 (± 11.50)	
Week 48 (N = 228, 116, 36)	10.4 (± 10.58)	10.8 (± 10.44)	8.4 (± 10.83)	
Week 72 (N = 208, 107, 33)	10.8 (± 9.55)	10.9 (± 10.64)	9.2 (± 11.44)	
Week 96 (N = 204, 96, 32)	10.3 (± 10.45)	11.7 (± 12.72)	9.5 (± 11.27)	
Week 108 (N = 194, 93, 33)	10.5 (± 10.49)	11.9 (± 12.08)	7.9 (± 10.62)	
Week 120 (N = 187, 87, 30)	11.0 (± 10.76)	11.6 (± 11.95)	10.7 (± 11.30)	
Week 132 (N = 182, 82, 30)	11.4 (± 10.13)	10.7 (± 11.47)	10.7 (± 10.36)	
Week 144 (N = 182, 75, 28)	9.9 (± 11.36)	11.2 (± 11.48)	9.8 (± 11.67)	
Week 156 (N = 179, 74, 28)	10.6 (± 10.94)	11.2 (± 11.48)	8.6 (± 12.32)	
Week 168 (N = 176, 73, 29)	10.8 (± 12.27)	10.6 (± 12.46)	11.4 (± 13.18)	
Week 180 (N = 178, 71, 29)	11.0 (± 11.59)	9.6 (± 13.56)	11.4 (± 12.45)	
Week 192 (N = 169, 72, 30)	10.8 (± 10.50)	10.9 (± 11.82)	11.5 (± 13.27)	
Week 204 (N = 164, 71, 30)	11.3 (± 10.56)	10.2 (± 13.01)	11.2 (± 12.70)	
Week 216 (N = 160, 65, 30)	11.4 (± 11.93)	10.4 (± 13.92)	10.1 (± 12.87)	
Week 228 (N = 152, 59, 30)	11.0 (± 11.25)	10.8 (± 14.00)	11.1 (± 13.18)	

Week 240 (N = 154, 62, 28)	11.9 (± 10.93)	11.4 (± 13.08)	9.2 (± 13.81)	
Week 252 (N = 150, 59, 30)	11.5 (± 10.83)	10.2 (± 13.68)	8.4 (± 13.48)	
Week 264 (N = 139, 55, 28)	11.6 (± 10.95)	10.7 (± 12.52)	7.8 (± 13.94)	
Week 276 (N = 129, 54, 27)	12.1 (± 10.98)	9.2 (± 13.02)	7.3 (± 13.02)	
Wek 288 (N = 137, 53, 28)	11.6 (± 10.88)	12.3 (± 11.83)	9.0 (± 13.94)	
Week 300 (N = 133, 52, 27)	11.1 (± 11.14)	9.7 (± 13.12)	7.0 (± 13.46)	
Week 312 (N = 136, 49, 27)	10.7 (± 11.24)	11.6 (± 12.67)	8.6 (± 14.35)	

Notes:

[64] - Open-label treated population with available data at Baseline and each time point

[65] - Open-label treated population with available data at Baseline and each time point

[66] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Instability Scale for RA (RA-WIS) Over Time

End point title	Change From Baseline in Work Instability Scale for RA (RA-WIS) Over Time

End point description:

RA-WIS is a tool to evaluate work instability (the consequence of a mismatch between an individual's functional ability and their work tasks). RA-WIS consists of 23 questions relating to the participant's functioning in their work environment, each answered as Yes or No. The total score is the number of questions answered Yes, and ranges from 0 to 23.
A score < 10 means low risk, scores between 10 and 17 indicate medium risk, and scores > 17 indicate high risk of work instability.
A negative change from Baseline indicates improvement in work instability.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192,
204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87[67]	53[68]	13[69]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 75, 45, 12)	-6.2 (± 5.55)	-3.3 (± 5.51)	-4.1 (± 3.00)	
Week 12 (N = 70, 43, 12)	-6.6 (± 6.16)	-4.0 (± 6.32)	-4.2 (± 3.35)	
Week 24 (N = 67, 41, 12)	-7.0 (± 6.51)	-4.6 (± 6.63)	-3.6 (± 3.53)	
Week 36 (N = 61, 42, 11)	-6.8 (± 6.29)	-4.6 (± 6.21)	-3.3 (± 6.18)	
Week 48 (N = 55, 40, 12)	-6.8 (± 5.94)	-5.0 (± 6.47)	-3.5 (± 4.98)	
Week 72 (N = 51, 39, 12)	-7.5 (± 6.83)	-4.8 (± 6.27)	-4.3 (± 4.10)	
Week 96 (N = 54, 37, 12)	-6.5 (± 6.72)	-6.3 (± 7.55)	-4.0 (± 4.18)	
Week 108 (N = 52, 32, 11)	-6.8 (± 6.80)	-6.5 (± 6.71)	-3.5 (± 4.80)	
Week 120 (N = 47, 31, 9)	-7.6 (± 6.66)	-5.1 (± 7.38)	-5.7 (± 4.44)	
Week 132 (N = 47, 29, 10)	-7.2 (± 6.04)	-5.6 (± 6.99)	-4.7 (± 3.47)	
Week 144 (N = 46, 26, 8)	-5.9 (± 6.51)	-5.6 (± 7.65)	-4.3 (± 3.41)	

Week 156 (N = 47, 25, 8)	-6.2 (± 7.13)	-4.3 (± 7.62)	-4.9 (± 3.72)	
Week 168 (N = 43, 24, 8)	-5.8 (± 6.01)	-4.3 (± 6.96)	-5.1 (± 6.69)	
Week 180 (N = 43, 24, 6)	-5.3 (± 6.61)	-3.5 (± 7.03)	-4.2 (± 3.19)	
Week 192 (N = 40, 24, 7)	-5.5 (± 6.42)	-3.5 (± 7.36)	-4.3 (± 2.93)	
Week 204 (N = 36, 23, 8)	-6.4 (± 7.06)	-3.7 (± 7.52)	-5.0 (± 3.78)	
Week 216 (N = 38, 23, 9)	-6.0 (± 7.55)	-3.4 (± 7.11)	-5.0 (± 2.92)	
Week 228 (N = 38, 18, 7)	-6.5 (± 7.16)	-1.9 (± 7.55)	-4.6 (± 4.24)	
Week 240 (N = 34, 21, 6)	-5.9 (± 7.05)	-3.1 (± 7.61)	-4.5 (± 4.09)	
Week 252 (N = 33, 18, 8)	-5.8 (± 6.43)	-2.0 (± 8.05)	-5.0 (± 3.70)	
Week 264 (N = 33, 20, 8)	-5.0 (± 6.53)	-3.4 (± 8.00)	-4.5 (± 3.89)	
Week 276 (N = 30, 18, 7)	-5.0 (± 6.74)	-2.7 (± 8.27)	-5.0 (± 2.52)	
Week 288 (N = 29, 17, 8)	-5.0 (± 7.05)	-4.8 (± 7.38)	-4.8 (± 3.45)	
Week 300 (N = 30, 15, 8)	-4.6 (± 7.23)	-4.3 (± 8.51)	-4.6 (± 4.07)	
Week 312 (N = 31, 15, 8)	-4.2 (± 7.00)	-3.9 (± 8.37)	-2.9 (± 4.45)	

Notes:

[67] - Open-label treated population who were working at Baseline and each visit and with available data
[68] - Open-label treated population who were working at Baseline and each visit and with available data
[69] - Open-label treated population who were working at Baseline and each visit and with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL-5D (EQ-5D) Index Over Time

End point title	Change From Baseline in EuroQoL-5D (EQ-5D) Index Over Time

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts. The first part (the descriptive system) assesses health in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which is rated on 5 levels of severity (1: no problem, 2: slight problems, 3: moderate problems, 4: severe problems, 5: extreme problems).
A health state index score was calculated from individual health profiles using a UK scoring algorithm. Health state index scores generally range from less than 0 (where 0 is the value of a health state equivalent to dead; negative values representing values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. The higher the score the better the health status. A positive change from baseline indicates improvement in health status.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304[70]	146[71]	37[72]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 278, 145, 36)	0.2 (± 0.24)	0.2 (± 0.27)	0.2 (± 0.18)	

Week 12 (N = 275, 142, 36)	0.2 (± 0.23)	0.2 (± 0.29)	0.2 (± 0.14)	
Week 24 (N = 256, 133, 36)	0.2 (± 0.23)	0.2 (± 0.28)	0.2 (± 0.16)	
Week 36 (N = 244, 126, 35)	0.2 (± 0.24)	0.2 (± 0.27)	0.2 (± 0.16)	
Week 48 (N = 228, 116, 36)	0.2 (± 0.25)	0.2 (± 0.31)	0.1 (± 0.20)	
Week 72 (N = 209, 107, 33)	0.2 (± 0.24)	0.2 (± 0.28)	0.2 (± 0.16)	
Week 96 (N = 204, 97, 32)	0.2 (± 0.25)	0.2 (± 0.28)	0.2 (± 0.15)	
Week 108 (N = 194, 93, 33)	00.2 (± 0.26)	0.2 (± 0.28)	0.1 (± 0.16)	
Week 120 (N = 187, 87, 30)	0.2 (± 0.26)	0.2 (± 0.27)	0.2 (± 0.16)	
Week 132 (N = 182, 82, 30)	0.2 (± 0.25)	0.2 (± 0.26)	0.2 (± 0.15)	
Week 144 (N = 182, 75, 28)	0.2 (± 0.28)	0.2 (± 0.27)	0.2 (± 0.17)	
Week 156 (N = 179, 74, 28)	0.2 (± 0.27)	0.2 (± 0.26)	0.1 (± 0.18)	
Week 168 (N = 176, 73, 29)	0.2 (± 0.29)	0.2 (± 0.28)	0.2 (± 0.20)	
Week 180 (N = 178, 71, 29)	0.2 (± 0.27)	0.2 (± 0.33)	0.2 (± 0.20)	
Week 192 (N = 169, 72, 30)	0.2 (± 0.27)	0.2 (± 0.27)	0.2 (± 0.20)	
Week 204 (N = 164, 71, 30)	0.2 (± 0.27)	0.2 (± 0.31)	0.2 (± 0.21)	
Week 216 (N = 160, 65, 30)	0.2 (± 0.29)	0.2 (± 0.30)	0.2 (± 0.18)	
Week 228 (N = 152, 59, 30)	0.2 (± 0.26)	0.2 (± 0.31)	0.1 (± 0.22)	
Week 240 (N = 154, 62, 28)	0.3 (± 0.29)	0.2 (± 0.26)	0.1 (± 0.22)	
Week 252 (N = 150, 59, 30)	0.2 (± 0.26)	0.2 (± 0.28)	0.2 (± 0.22)	
Week 264 (N = 139, 55, 28)	0.3 (± 0.29)	0.2 (± 0.25)	0.1 (± 0.23)	
Week 276 (N = 129, 54, 27)	0.2 (± 0.30)	0.2 (± 0.26)	0.1 (± 0.22)	
Week 288 (N = 137, 53, 28)	0.3 (± 0.27)	0.2 (± 0.27)	0.1 (± 0.23)	
Week 300 (N = 133, 52, 27)	0.2 (± 0.28)	0.2 (± 0.27)	0.1 (± 0.19)	
Week 312 (N = 136, 49, 27)	0.2 (± 0.29)	0.2 (± 0.26)	0.1 (± 0.25)	

Notes:

[70] - Open-label treated population with available data at Baseline and each time point

[71] - Open-label treated population with available data at Baseline and each time point

[72] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL-5D VAS Score Over Time

End point title	Change From Baseline in EuroQoL-5D VAS Score Over Time

End point description:

The EQ-5D-5L is a generic measure of health status consisting of two parts. The second part of the questionnaire consists of a visual analog scale (VAS) on which the participant rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health).
A positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline (of the preceding RCT study) and Weeks 6, 12, 24, 36, 48, 72, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 216, 228, 240, 252, 264, 276, 288, 300, and 312.

End point values	Upadacitinib Never Titrated	Upadacitinib Titrated Up and Not Down	Upadacitinib Titrated Up and Down	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304[73]	146[74]	37[75]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 6 (N = 278, 145, 36)	23.7 (± 25.21)	14.4 (± 24.94)	21.6 (± 20.49)	
Week 12 (N = 275, 142, 36)	26.0 (± 25.62)	15.9 (± 25.83)	19.4 (± 25.07)	
Week 24 (N = 256, 133, 36)	27.5 (± 25.24)	16.8 (± 27.31)	20.7 (± 20.67)	
Week 36 (N = 244, 126, 35)	27.0 (± 26.29)	18.6 (± 27.10)	18.6 (± 21.05)	
Week 48 (N = 228, 116, 36)	25.9 (± 26.87)	19.1 (± 28.61)	19.7 (± 21.07)	
Week 72 (N = 209, 107, 33)	28.0 (± 24.36)	21.9 (± 26.33)	26.7 (± 21.43)	
Week 96 (N = 204, 97, 32)	27.5 (± 26.86)	22.4 (± 27.73)	25.4 (± 19.25)	
Week 108 (N = 194, 93, 33)	28.8 (± 25.72)	23.2 (± 25.81)	20.5 (± 19.06)	
Week 120 (N = 187, 87, 30)	28.4 (± 27.22)	23.7 (± 25.36)	27.2 (± 23.54)	
Week 132 (N = 182, 82, 30)	26.3 (± 28.75)	23.5 (± 26.23)	28.1 (± 19.62)	
Week 144 (N = 182, 75, 28)	28.6 (± 26.71)	23.5 (± 24.29)	24.7 (± 25.32)	
Week 156 (N = 179, 74, 28)	29.9 (± 25.48)	22.5 (± 24.62)	22.1 (± 23.52)	
Week 168 (N = 176, 73, 29)	30.3 (± 25.29)	22.6 (± 23.74)	28.1 (± 24.06)	
Week 180 (N = 178, 71, 29)	30.0 (± 24.30)	22.0 (± 27.24)	27.0 (± 21.68)	
Week 192 (N = 169, 72, 30)	29.7 (± 24.65)	23.6 (± 26.41)	30.8 (± 21.96)	
Week 204 (N = 164, 71, 30)	32.0 (± 24.41)	23.1 (± 27.13)	30.7 (± 22.99)	
Week 216 (N = 160, 65, 30)	30.0 (± 26.93)	24.0 (± 26.40)	28.0 (± 21.73)	
Week 228 (N = 152, 59, 30)	31.6 (± 24.92)	19.7 (± 26.70)	29.5 (± 23.85)	
Week 240 (N = 154, 62, 28)	31.3 (± 26.18)	21.9 (± 25.62)	28.4 (± 26.55)	
Week 252 (N = 150, 59, 30)	31.2 (± 24.46)	22.8 (± 26.74)	25.6 (± 23.74)	
Week 264 (N = 139, 55, 28)	30.8 (± 25.30)	22.2 (± 23.60)	21.9 (± 24.81)	
Week 276 (N = 129, 54, 27)	32.4 (± 23.37)	20.5 (± 25.68)	25.4 (± 20.62)	
Week 288 (N = 137, 53, 28)	32.3 (± 24.66)	24.6 (± 25.54)	25.3 (± 22.57)	
Week 300 (N = 133, 52, 27)	30.5 (± 24.39)	20.4 (± 27.31)	23.6 (± 17.27)	
Week 312 (N = 136, 49, 27)	31.2 (± 25.15)	25.8 (± 24.81)	24.1 (± 25.18)	

Notes:

[73] - Open-label treated population with available data at Baseline and each time point

[74] - Open-label treated population with available data at Baseline and each time point

[75] - Open-label treated population with available data at Baseline and each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Satisfactory Humoral Response to PCV-13 12 Weeks After Vaccination

End point title	Percentage of Participants With Satisfactory Humoral Response to PCV-13 12 Weeks After Vaccination

End point description:

Satisfactory humoral response is defined as greater than or equal to 2-fold increase in antibody concentration from the vaccination Baseline in at least 6 out of the 12 pneumococcal antigens 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).

End point type	Secondary

End point timeframe:

Vaccination Baseline and 12 weeks after vaccination

End point values	Upadacitinib 15 mg + PCV-13	Upadacitinib 30 mg + PCV-13		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79[76]	22[77]		
Units: percentage of participants				
number (confidence interval 95%)	64.6 (54.0 to 75.1)	54.5 (33.7 to 75.4)		

Notes:

[76] - Sub-study FAS with available data at the Week 12 visit of the sub-study

[77] - Sub-study FAS with available data at the Week 12 visit of the sub-study

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) of Anti-pneumococcal Antibody Levels to Each of the 12 Pneumococcal Antigens 4 and 12 Weeks After Vaccination

End point title	Geometric Mean Fold Rise (GMFR) of Anti-pneumococcal Antibody Levels to Each of the 12 Pneumococcal Antigens 4 and 12 Weeks After Vaccination

End point description:

End point type	Secondary

End point timeframe:

Vaccination Baseline and 4 and 12 weeks after vaccination

End point values	Upadacitinib 15 mg + PCV-13	Upadacitinib 30 mg + PCV-13		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83[78]	23[79]		
Units: fold-rise				
geometric mean (confidence interval 95%)				
Antigen 1: Week 4	7.90 (6.096 to 10.244)	6.53 (3.985 to 10.684)		
Antigen 1: Week 12	8.07 (6.158 to 10.567)	6.54 (3.922 to 10.911)		
Antigen 3: Week 4	2.59 (2.088 to 3.205)	2.30 (1.530 to 3.467)		
Antigen 3: Week 12	2.26 (1.805 to 2.824)	2.24 (1.464 to 3.431)		
Antigen 4: Week 4	5.61 (4.279 to 7.362)	3.82 (2.283 to 6.402)		
Antigen 4: Week 12	5.17 (3.888 to 6.885)	3.39 (1.970 to 5.826)		
Antigen 5: Week 4	1.90 (1.521 to 2.366)	1.60 (1.050 to 2.431)		
Antigen 5: Week 12	1.84 (1.485 to 2.288)	1.57 (1.043 to 2.367)		

Antigen 6B: Week 4	4.50 (3.325 to 6.077)	3.10 (1.748 to 5.511)		
Antigen 6B: Week 12	3.90 (2.801 to 5.436)	3.25 (1.732 to 6.092)		
Antigen 7F: Week 4	3.58 (2.824 to 4.548)	2.83 (1.797 to 4.446)		
Antigen 7F: Week 12	3.30 (2.552 to 4.255)	3.02 (1.856 to 4.897)		
Antigen 9V: Week 4	5.69 (4.260 to 7.611)	2.76 (1.588 to 4.794)		
Antigen 9V: Week 12	6.18 (4.583 to 8.325)	2.91 (1.649 to 5.138)		
Antigen 14: Week 4	2.97 (2.373 to 3.723)	2.42 (1.573 to 3.707)		
Antigen 14: Week 12	2.84 (2.231 to 3.613)	2.41 (1.524 to 3.804)		
Antigen 18C: Week 4	4.52 (3.526 to 5.801)	3.23 (2.009 to 5.179)		
Antigen 18C: Week 12	4.42 (3.443 to 5.670)	3.53 (2.201 to 5.666)		
Antigen 19A: Week 4	1.47 (1.264 to 1.702)	1.12 (0.844 to 1.485)		
Antigen 19A: Week 12	1.44 (1.245 to 1.666)	1.15 (0.876 to 1.521)		
Antigen 19F: Week 4	2.27 (1.834 to 2.808)	2.32 (1.549 to 3.476)		
Antigen 19F: Week 12	2.17 (1.761 to 2.671)	1.99 (1.344 to 2.958)		
Antigen 23F: Week 4	4.32 (3.291 to 5.672)	3.11 (1.855 to 5.218)		
Antigen 23F: Week 12	4.06 (3.048 to 5.413)	3.29 (1.908 to 5.666)		

Notes:

[78] - Sub-study full analysis set with available data at each time point; N=79 at Week 12

[79] - Sub-study full analysis set with available data at each time point; N= 22 at Week 12

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of open-label upadacitinib up to 30 days after the last dose, up to 316 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Upadacitinib 6 mg BID/15 mg QD
Reporting group description:	
Participants received upadacitinib 6 mg BID. From January 2017 participants were transitioned to 15 mg upadacitinib QD. Includes events that occurred until the time of up-titration for participants who were up-titrated.	
Reporting group title	Upadacitinib 12 mg BID/30 mg QD
Reporting group description:	
Participants received upadacitinib 12 mg BID. From January 2017 participants were transitioned to 30 mg upadacitinib QD. Includes events that occurred from the time of up-titration until time of down titration to 6 mg BID/15 mg QD for participants who titrated up and back down.	
Reporting group title	Upadacitinib 6 mg BID/15 mg QD Post Down-titration
Reporting group description:	
Participants who down-titrated to 6 mg BID/15 mg QD after up-titration to 15 mg BID/30 mg QD. Includes events that occurred after down titration.	

Serious adverse events	Upadacitinib 6 mg BID/15 mg QD	Upadacitinib 12 mg BID/30 mg QD	Upadacitinib 6 mg BID/15 mg QD Post Down-titration
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 493 (13.79%)	42 / 187 (22.46%)	5 / 38 (13.16%)
number of deaths (all causes)	5	3	0
number of deaths resulting from adverse events	3	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
CLEAR CELL RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
ENDOMETRIAL CANCER			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
HODGKIN'S DISEASE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE LOBULAR BREAST CARCINOMA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
INVASIVE PAPILLARY BREAST CARCINOMA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
LUNG ADENOCARCINOMA STAGE I			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
NON-SMALL CELL LUNG CANCER			

subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
PAPILLARY THYROID CANCER			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
SEBACEOUS CARCINOMA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PROSTATE CANCER			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
SQUAMOUS CELL CARCINOMA OF LUNG			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
SQUAMOUS CELL CARCINOMA OF THE CERVIX			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
THYROID B-CELL LYMPHOMA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	3 / 493 (0.61%)	2 / 187 (1.07%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY THROMBOSIS			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PERIPHERAL ARTERY STENOSIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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			
CHEST PAIN			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
DEATH			
subjects affected / exposed	2 / 493 (0.41%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Reproductive system and breast disorders			
CERVICAL DYSPLASIA			
subjects affected / exposed	2 / 493 (0.41%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROSALPINX			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
EPISTAXIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
LUNG INFILTRATION			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PARANASAL CYST			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PLEURAL EFFUSION			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PLEURISY			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PNEUMONITIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 493 (0.41%)	2 / 187 (1.07%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SLEEP APNOEA SYNDROME			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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 FAILURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
ANXIETY			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
DISSOCIATIVE DISORDER			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
DEPRESSION			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE LOOSENING			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
CONTUSION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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

FALL			
subjects affected / exposed	1 / 493 (0.20%)	2 / 187 (1.07%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
FEMUR FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOREARM FRACTURE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAND FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
HIP FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	2 / 493 (0.41%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCARCERATED INCISIONAL HERNIA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
MULTIPLE FRACTURES			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE INJURIES			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERDOSE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
POST PROCEDURAL DISCHARGE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
RADIUS FRACTURE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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 LACERATION			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
SKULL FRACTURED BASE			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
TENDON RUPTURE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 493 (0.81%)	0 / 187 (0.00%)	0 / 38 (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
ANGINA PECTORIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
ANGINA UNSTABLE			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AORTIC VALVE INCOMPETENCE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
ATRIAL FLUTTER			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK SECOND DEGREE			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
CARDIOMYOPATHY			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
CORONARY ARTERY DISSECTION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STRESS CARDIOMYOPATHY			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
Nervous system disorders			
BRAIN STEM INFARCTION			

subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
CEREBRAL INFARCTION			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
HEADACHE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
DIZZINESS			
subjects affected / exposed	2 / 493 (0.41%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LACUNAR INFARCTION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
INTRACRANIAL ANEURYSM			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
OCCIPITAL NEURALGIA			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
SCIATICA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
SYNCOPE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
Blood and lymphatic system disorders			
BLOOD LOSS ANAEMIA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
Ear and labyrinth disorders			
VESTIBULAR DISORDER			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
Eye disorders			
CORNEAL PERFORATION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
GLAUCOMA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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

MACULAR HOLE			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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			
ENTEROCOLITIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
VOMITING			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
HEPATITIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
HEPATOTOXICITY			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
SKIN ULCER			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
BLADDER PROLAPSE			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
GOITRE			

subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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			
INTERVERTEBRAL DISC COMPRESSION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
ARTHRALGIA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	2 / 493 (0.41%)	0 / 187 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	4 / 493 (0.81%)	3 / 187 (1.60%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SYNOVITIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
SPONDYLOLISTHESIS			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
BRONCHITIS			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS			
subjects affected / exposed	1 / 493 (0.20%)	3 / 187 (1.60%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 493 (0.00%)	2 / 187 (1.07%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
ENDOMETRITIS			

subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
GASTROENTERITIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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 VIRAL			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
HEPATITIS A			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
HERPES ZOSTER			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HISTOPLASMOSIS DISSEMINATED			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
INFLUENZA			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
LATENT TUBERCULOSIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
PNEUMONIA			

subjects affected / exposed	7 / 493 (1.42%)	3 / 187 (1.60%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	2 / 7	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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 TRACT INFECTION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
SEPSIS			
subjects affected / exposed	0 / 493 (0.00%)	2 / 187 (1.07%)	0 / 38 (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
SOFT TISSUE INFECTION			
subjects affected / exposed	0 / 493 (0.00%)	1 / 187 (0.53%)	0 / 38 (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
TUBERCULOSIS			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
VARICELLA			
subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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
VARICELLA ZOSTER VIRUS INFECTION			

subjects affected / exposed	1 / 493 (0.20%)	0 / 187 (0.00%)	0 / 38 (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			
HYPONATRAEMIA			
subjects affected / exposed	0 / 493 (0.00%)	0 / 187 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
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	Upadacitinib 6 mg BID/15 mg QD	Upadacitinib 12 mg BID/30 mg QD	Upadacitinib 6 mg BID/15 mg QD Post Down-titration
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 493 (47.26%)	113 / 187 (60.43%)	23 / 38 (60.53%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	22 / 493 (4.46%)	19 / 187 (10.16%)	1 / 38 (2.63%)
occurrences (all)	23	19	1
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	6 / 493 (1.22%)	10 / 187 (5.35%)	2 / 38 (5.26%)
occurrences (all)	9	11	2
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	14 / 493 (2.84%)	10 / 187 (5.35%)	1 / 38 (2.63%)
occurrences (all)	14	11	2
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	12 / 493 (2.43%)	4 / 187 (2.14%)	3 / 38 (7.89%)
occurrences (all)	15	4	4
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	16 / 493 (3.25%)	5 / 187 (2.67%)	2 / 38 (5.26%)
occurrences (all)	17	5	3
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	34 / 493 (6.90%)	17 / 187 (9.09%)	3 / 38 (7.89%)
occurrences (all)	44	27	4
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	7 / 493 (1.42%)	14 / 187 (7.49%)	1 / 38 (2.63%)
occurrences (all)	8	20	1
Nervous system disorders			
HEADACHE			
subjects affected / exposed	18 / 493 (3.65%)	5 / 187 (2.67%)	3 / 38 (7.89%)
occurrences (all)	23	7	3
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed	15 / 493 (3.04%)	5 / 187 (2.67%)	2 / 38 (5.26%)
occurrences (all)	17	6	2
ANAEMIA			
subjects affected / exposed	7 / 493 (1.42%)	11 / 187 (5.88%)	1 / 38 (2.63%)
occurrences (all)	7	12	1
NEUTROPENIA			
subjects affected / exposed	10 / 493 (2.03%)	2 / 187 (1.07%)	2 / 38 (5.26%)
occurrences (all)	13	3	2
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	7 / 493 (1.42%)	10 / 187 (5.35%)	0 / 38 (0.00%)
occurrences (all)	7	11	0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	4 / 493 (0.81%)	5 / 187 (2.67%)	2 / 38 (5.26%)
occurrences (all)	4	5	2
ROSACEA			
subjects affected / exposed	4 / 493 (0.81%)	2 / 187 (1.07%)	2 / 38 (5.26%)
occurrences (all)	4	2	2
Renal and urinary disorders			
RENAL COLIC			
subjects affected / exposed	0 / 493 (0.00%)	2 / 187 (1.07%)	2 / 38 (5.26%)
occurrences (all)	0	2	3
NEPHROLITHIASIS			

subjects affected / exposed	7 / 493 (1.42%)	1 / 187 (0.53%)	2 / 38 (5.26%)
occurrences (all)	10	1	3
Musculoskeletal and connective tissue disorders			
RHEUMATOID ARTHRITIS			
subjects affected / exposed	21 / 493 (4.26%)	21 / 187 (11.23%)	0 / 38 (0.00%)
occurrences (all)	32	35	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	42 / 493 (8.52%)	14 / 187 (7.49%)	6 / 38 (15.79%)
occurrences (all)	66	23	8
LATENT TUBERCULOSIS			
subjects affected / exposed	10 / 493 (2.03%)	2 / 187 (1.07%)	2 / 38 (5.26%)
occurrences (all)	10	2	2
HERPES ZOSTER			
subjects affected / exposed	22 / 493 (4.46%)	21 / 187 (11.23%)	3 / 38 (7.89%)
occurrences (all)	23	24	3
NASOPHARYNGITIS			
subjects affected / exposed	47 / 493 (9.53%)	16 / 187 (8.56%)	3 / 38 (7.89%)
occurrences (all)	75	19	3
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 493 (0.20%)	1 / 187 (0.53%)	3 / 38 (7.89%)
occurrences (all)	1	1	4
PHARYNGITIS			
subjects affected / exposed	10 / 493 (2.03%)	3 / 187 (1.60%)	2 / 38 (5.26%)
occurrences (all)	12	3	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	49 / 493 (9.94%)	38 / 187 (20.32%)	3 / 38 (7.89%)
occurrences (all)	71	63	8
SINUSITIS			
subjects affected / exposed	13 / 493 (2.64%)	14 / 187 (7.49%)	0 / 38 (0.00%)
occurrences (all)	15	24	0
URINARY TRACT INFECTION			
subjects affected / exposed	47 / 493 (9.53%)	28 / 187 (14.97%)	3 / 38 (7.89%)
occurrences (all)	84	54	6
VIRAL UPPER RESPIRATORY TRACT			

INFECTION			
subjects affected / exposed	3 / 493 (0.61%)	3 / 187 (1.60%)	2 / 38 (5.26%)
occurrences (all)	3	3	2
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	29 / 493 (5.88%)	17 / 187 (9.09%)	3 / 38 (7.89%)
occurrences (all)	35	18	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2014	• Revised anticipated number of sites expected to participate in the study since additional sites were being added to RCTs. • Updated contact information to revise clinical study team members and create a back-up emergency phone number for the Study Designated Physician. • Revised collection of PK samples to the preferred timeframe of 1 to 8 hours since collection of blood samples was expected to be the most informative timeframe in population PK analysis based on ABT-494 PK properties. • Updated PK variables section to avoid redundancy about sample collection times and to describe the PK variable that were to be estimated. • Revised text to provide a description of the population PK and exposure-response analyses. • Revised text to clarify the definition of baseline for purposes of statistical analyses. • Revised text on the acceptable concomitant therapy during the study. • Updated text to include the addition of a gap period to allow greater flexibility of timing for patients who are considering entering into the OLE from completed RCT.
12 January 2016	• Revised text to update the actual number of sites and subjects participating in the study since no additional sites were to be added given both RCTs were complete. • Extended the length of the treatment period to a maximum of 264 weeks to allow sufficient exposure to ABT-494 and collect additional safety data. • Updated dosage formulation to change from immediate-release capsule formulation to modified release tablet formulation based on extrapolation of pre-clinical efficacy models and analyses of PK, pharmacodynamic, safety, and efficacy data from the Phase 1 studies in healthy volunteers and completed Phase 2b RCTs in RA subjects. • Revised text in Section 1.2 and Section 1.3 to be consistent with Amendment 2 revisions. • Added Contraception Recommendations and Pregnancy Testing. • Revised text to apply administrative changes throughout the protocol, to improve consistency and readability, and/or provide clarification. • Revised text to remove Handling /Processing of Samples, and Disposition of Samples, since the Lab manual was to be used for detailed instructions regarding sample collection, processing, and shipment.

10 November 2017	• Applied administrative changes to improve consistency and readability, and/or clarity. • Changed ABT-494 to upadacitinib throughout. • Updated overall study design and plan to reflect the addition of the Prevnar 13®. • Revised Inclusion Criterion 4 to reflect that upadacitinib in non-genotoxic, showed no testicular findings in chronic animal toxicology studies and had no impact on male or female fertility. • Added clarification on requirements for contraception for females of child-bearing potential status changes during the study. Updated required duration of contraception and sperm donation waiting period to reflect new data obtained from chronic animal toxicology studies. • Added clarification on indeterminate QuantiFERON tuberculosis (TB) test results to prevent unnecessary initiation of TB prophylaxis. Updated Informed Consent to reflect that written consent was needed to participate in the vaccine sub-study. Updated 'Pregnancy Test' to reflect pregnancy testing requirements should child-bearing status change. • Updated examples of commonly used strong CYP3A inhibitors and inducers. • Added AEs of special interest (AESIs), including embolic and thrombotic events, based on reported data for JAK inhibitors. • Updated Management of Select Laboratory Abnormalities to properly reflect the then current content of Specific Toxicity Management Guidelines for Abnormal Laboratory Values to improve readability and clarity. Added clarification on criteria for discontinuation due to ECG abnormality, updated toxicity management guidelines for serum creatine and and for creatine phosphokinase (CPK) laboratory values. • Updated definition for assessing the relationship of AEs to use of study drug. • Updated list of Protocol Signatories for Amendment 3. • Added Appendix N to outline local requirements for the UK. • Added Appendix O to outline the methods, procedures and statistical analyses pertaining to the Prevnar 13® Vaccine.
13 February 2019	• Revised text to apply administrative changes throughout the protocol to improve consistency and readability, and/or provide clarity. • Extended OLE study to add an additional 4 subject visits and revised text to improve consistency and readability, and/or provide clarity. • Revised text to improve time points of TB testing and 12 Lead ECG expectations for clarity purposes in Table 2 Study Activities Table.

17 December 2019	• Revised text to include administrative changes to improve consistency and readability and/or clarity. • Clarified dosing for all subjects: starting with Amendment 5, subjects receiving 30 mg QD upadacitinib were to have the option to decrease to the 15 mg QD dose based on investigator's discretion. • Revised text to include Emergency Medical Contact. • Added guidance in Prohibited Therapy for use of live vaccine administration to align with guidelines on live vaccine administration in the setting of immunosuppressive. • Revised Contraception Recommendations to remove male contraception requirements, as based on the calculated safety margins for human fetal exposure with seminal fluid transfer, risks to a fetus from a male taking the study drug were not anticipated. • Revised study procedures to provide guidance for interpretation of positive annual TB testing results in low-risk subjects and added the ability to retest locally to confirm central laboratory result. Added use of Interferon Gamma Release Assay as a substitute for local TB testing since it is an equivalent assay to the QuantiFERON-TB Gold Plus. Specified that only subjects with newly identified TB risks were to be subject to chest x-rays. • Clarified that restart of study drug after an interruption of > 30 consecutive days was at the discretion of the investigator. • Added an additional safety precaution for subjects given the recent concerns raised for the JAK inhibitor class regarding risk of venous thromboembolic events (VTE). • Clarified study drug accountability procedures consistent with current monitoring plan. • Clarified throughout protocol that all cardiac, embolic and thrombotic events were to be adjudicated. • Updated text to be consistent with the Guidance to investigator in the recently updated Upadacitinib Investigator Brochure. Updated AST or ALT parameters for management. Updated study drug interruption for elective surgery to at least 1 week prior to surgery.
01 December 2020	• Updated sponsor Emergency/Medical Contact. • Included evaluation of the benefit and risk to subjects participating in the study relative to COVID-19. • Added provisions for virtual or alternative locations for study visits in the event of a pandemic situation like COVID-19 or any state of emergency. • Revised Prohibited Therapy to update the list of examples of commonly used strong cytochrome 3A inducers. • Specified that the questionnaires, the Patient's Global Assessment of Disease Activity VAS, Patient's Assessment of Pain VAS and Health Outcomes Questionnaire, and PhGA VAS were not eligible for completion by virtual interview. • Added provision allowing the complete physical examination to be performed at the next earliest feasible visit. • Added provision allowing the TJC and SJC to be performed at the next earliest feasible visit by the independent joint assessor. • Added provision allowing the urine pregnancy test to be performed at a local laboratory or at home. • Specified that chest X-rays could be performed at the next earliest feasible visit unless the investigator had determined that a chest x-ray was required to ensure that it was safe to continue study drug administration. • Specified that the 12-Lead ECG could be performed at the next earliest feasible visit unless the investigator had determined that an ECG was required to ensure that it was safe to continue study drug administration. • Added provision to allow the laboratory testing for clinical laboratory tests at an alternate local facility in the event that a state of emergency or pandemic prevented the subject from performing the central laboratory tests and added requirements to allow the study drug dispensation when laboratory tests were performed at a local laboratory. • Added provision allowing Direct-to-Patient (DTP) shipment of study drug and study ancillaries. • Added new section Optional Home Healthcare Service.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported