Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis

Summary

EudraCT number	2017-000431-14
Trial protocol	FR DK DE FI CZ GB ES PT NL BE HU PL SE HR
Global end of trial date	17 February 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023

Trial information

Trial identification

Sponsor protocol code	M16-098

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03178487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of upadacitinib in participants with active ankylosing spondylitis (AS) who have had an inadequate response to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) or intolerance to or a contraindication for NSAIDs, and who are naïve to biologic disease-modifying anti-rheumatic drugs (bDMARD).

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 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Portugal: 11
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 14

Worldwide total number of subjects	187
EEA total number of subjects	128

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)	176
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled between October 24, 2017, and September 10, 2018 at 62 sites in 20 countries in North America, Eastern and Western Europe, Asia, and Oceania.
This study consists of a 14-week double-blind treatment period (Period 1) and a 90-week long-term extension period (Period 2) for participants who completed Period 1.

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio to one of two treatment groups. Randomization was stratified by screening concentrations of high-sensitivity C-reactive protein (hsCRP; ≤ upper limit of normal [ULN] vs > ULN; where the ULN is 2.87 mg/L) and geographical region (USA and Canada, Japan, rest of the world).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo orally once a day for 14 weeks in Period 1.

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

Dosage and administration details:

Placebo matching tablets taken orally once a day.

Arm title	Upadacitinib 15 mg

Arm description:

Participants received 15 mg upadacitinib orally once a day for 14 weeks in Period 1.

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

Dosage and administration details:

Tablets taken orally once a day.

Number of subjects in period 1	Placebo	Upadacitinib 15 mg
Started	94	93
Received Treatment	94	93
Completed	90	89
Not completed	4	4
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	2
Other	-	1
Lost to follow-up	1	-

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo / Upadacitinib 15 mg

Arm description:

Participants randomized to receive placebo in Period 1 received upadacitinib 15 mg orally once a day for 90 weeks in Period 2.

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 orally once a day.

Arm title	Upadacitinib 15 mg / Upadacitinib 15 mg

Arm description:

Participants randomized to receive upadacitinib in Period 1 continued to receive upadacitinib 15 mg orally once a day for 90 weeks in Period 2.

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 orally once a day.

Number of subjects in period 2	Placebo / Upadacitinib 15 mg	Upadacitinib 15 mg / Upadacitinib 15 mg
Started	90	89
Received Treatment	89	89
Completed	69	70
Not completed	21	19
Consent withdrawn by subject	6	6
Adverse event, non-fatal	4	4
COVID-19 Logistical Restrictions	1	-
Other	8	7
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo orally once a day for 14 weeks in Period 1.	
Reporting group title	Upadacitinib 15 mg
Reporting group description:	
Participants received 15 mg upadacitinib orally once a day for 14 weeks in Period 1.	

Reporting group values	Placebo	Upadacitinib 15 mg	Total
Number of subjects	94	93	187
Age categorical Units: Subjects			
< 40 years	39	28	67
40 - 64 years	53	56	109
≥ 65 years	2	9	11
Age continuous Units: years			
arithmetic mean	43.7	47.0	
standard deviation	± 12.07	± 12.78	-
Gender categorical Units: Subjects			
Female	25	30	55
Male	69	63	132
Ethnicity Units: Subjects			
Hispanic or Latino	5	4	9
Not Hispanic or Latino	89	89	178
Race Units: Subjects			
White	76	79	155
Black or African American	2	1	3
Asian	16	13	29
Region Units: Subjects			
USA and Canada	10	9	19
Western Europe	33	30	63
Eastern Europe	34	36	70
Japan	7	6	13
South Korea	7	6	13
Australia and New Zealand	3	6	9
High-sensitivity C-reactive Protein (hsCRP) Level at Screening			
The Screening level of hsCRP was a randomization stratification factor. The hsCRP upper limit of normal (ULN) = 2.87 mg/L.			
Units: Subjects			
> upper limit of normal	68	67	135
≤ upper limit of normal	26	26	52

Duration Since Ankylosing Spondylitis Diagnosis			
Units: years			
arithmetic mean	6.0	7.8	
standard deviation	± 6.79	± 10.64	-
Duration of Ankylosing Spondylitis Symptoms			
Units: years			
arithmetic mean	14.0	14.8	
standard deviation	± 9.86	± 11.64	-
Patient's Global Assessment of Disease Activity (PtGA)			
Assessed by the participant using a numeric rating scale (NRS) ranging from 0 (No activity) to 10 (Severe activity). 94 and 91 participants had available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	6.8	6.6	
standard deviation	± 1.66	± 1.81	-
Patient's Assessment of Total Back Pain			
Total back pain was assessed by the participant on a NRS from 0 (no pain) to 10 (most severe pain). 94 and 92 participants had available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	6.7	6.8	
standard deviation	± 1.78	± 1.77	-
Bath Ankylosing Spondylitis Functional Index			
The Bath Ankylosing Spondylitis Functional Index (BASFI) is used to determine the degree of functional limitation in patients with AS. BASFI consists of 10 questions assessing participants' ability to perform activities, each scored on a NRS ranging from 0 (easy to perform activity) to 10 (impossible to perform activity). The overall score is the mean of the 10 items and ranges from 0 to 10 with higher score indicating more functional limitations. 94 and 91 participants had available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	5.5	5.4	
standard deviation	± 2.17	± 2.36	-
Inflammation			
Inflammation was measured by the mean of the two morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration). 94 and 92 particiapnts had available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	6.7	6.5	
standard deviation	± 1.90	± 1.99	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo orally once a day for 14 weeks in Period 1.	
Reporting group title	Upadacitinib 15 mg
Reporting group description:	
Participants received 15 mg upadacitinib orally once a day for 14 weeks in Period 1.	
Reporting group title	Placebo / Upadacitinib 15 mg
Reporting group description:	
Participants randomized to receive placebo in Period 1 received upadacitinib 15 mg orally once a day for 90 weeks in Period 2.	
Reporting group title	Upadacitinib 15 mg / Upadacitinib 15 mg
Reporting group description:	
Participants randomized to receive upadacitinib in Period 1 continued to receive upadacitinib 15 mg orally once a day for 90 weeks in Period 2.	

Primary: Percentage of Participants With Assessment of SpondyloArthritis International Society (ASAS) 40 Response at Week 14

End point title	Percentage of Participants With Assessment of SpondyloArthritis International Society (ASAS) 40 Response at Week 14
End point description:	
ASAS 40 response was defined as improvement of ≥ 40% relative to Baseline and absolute improvement of ≥ 2 units in ≥ 3 of the following 4 domains with no deterioration (a net worsening of > 0 units) in the potential remaining domain: 1) Patient's global assessment of disease activity, measured on a NRS from 0 - 10 (severe activity); 2) Pain, measured by the total back pain NRS from 0 - 10 (most severe pain); 3) Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI), consisting of 10 items assessing participants' ability to perform activities each on an NRS from 0 (easy) - 10 (impossible); 4) Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/≥ 2 hours duration). Participants with missing data or who discontinued study drug prior to Week 14 were counted as non-responders.	
End point type	Primary
End point timeframe:	
Baseline and Week 14	

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[1]	93[2]		
Units: percentage of participants				
number (confidence interval 95%)	25.5 (16.7 to 34.3)	51.6 (41.5 to 61.8)		

Notes:

[1] - Full analysis set (all randomized participants who received at least one dose of study drug)

[2] - Full analysis set

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.6
upper limit	39.5

Notes:

[3] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint.

[4] - Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor of Screening hsCRP level.

Secondary: Change From Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 14

End point title	Change From Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 14

End point description:

ASDAS is a composite index to assess disease activity in Ankylosing Spondylitis. ASDAS combines the following 5 disease activity variables using a weighted formula:
1. Patient's assessment of total back pain (BASDAI Question 2; NRS from 0 - 10 [very severe])
2. Patient global assessment of disease activity (NRS from 0 [no activity] - 10 [severe activity])
3. Peripheral pain/swelling (BASDAI Question 3; NRS from 0 - 10 [very severe])
4. Duration of morning stiffness (BASDAI Question 6; NRS from 0 [0 hours] - 10 [2 or more hours])
5. hs-CRP in mg/L.

The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS include Inactive disease (ASDAS < 1.3) and very high disease (ASDAS > 3.5). A negative change from Baseline score indicates improvement in disease activity.
A mixed effect model repeat measurement (MMRM) analysis with longitudinal data from observed cases up to Week 14 was used.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84[5]	84[6]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.54 (-0.71 to -0.37)	-1.45 (-1.62 to -1.28)		

Notes:

[5] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

[6] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in ASDAS
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	-0.68

Notes:

[7] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint.

[8] - MMRM model includes treatment, visit, treatment-by-visit interaction as fixed effects and Screening hsCRP level and Baseline value as covariates.

Secondary: Change From Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Score for the Spine at Week 14

End point title	Change From Baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic Resonance Imaging (MRI) Score for the Spine at Week 14

End point description:

The entire spine was evaluated for active inflammation (bone marrow edema) and 6 discovertebral units (DVU) representing the most abnormal DVUs were selected to calculate the SPARCC MRI Spine score. For each of the 6 DVUs, 3 consecutive sagittal slices were assessed in 4 quadrants to evaluate the extent of inflammation in three dimensions. Each quadrant was scored for the presence (1) or absence (0) of edema. If edema was present in at least 1 quadrant of a DVU slice, it was also scored for intensity and depth of the edema representing that slice: An additional score of 1 was assigned if an intense signal was seen in any quadrant on a DVU slice. Slices that included a lesion demonstrating continuous increased signal of depth ≥ 1 cm extending from the endplate were scored as an additional 1 per slice. The maximum (worst) overall score for all 6 DVUs is 108.
MRI data up to 3 days post first dose (for Baseline) and up to first dose of period 2 for Week 14 were included in the anlaysis.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[9]	68[10]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.22 (-2.01 to 1.57)	-6.93 (-8.58 to -5.28)		

Notes:

[9] - Full analysis set with available MRI data during pre-specified time window

[10] - Full analysis set with available MRI data during pre-specified time window

Statistical analyses

Statistical analysis title	Analysis of Change in SPARCC MRI Spine Score
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-6.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.01
upper limit	-4.41

Notes:

[11] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint.

[12] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Secondary: Percentage of Participants With Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at Week 14

End point title	Percentage of Participants With Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at Week 14

End point description:

The BASDAI assesses disease activity by asking the participant to answer 6 questions (each on an 11 point numeric rating scale [NRS]) pertaining to symptoms experienced for the past week. For Questions 1 to 5 (level of fatigue/tiredness, level of AS neck, back or hip pain, level of pain/swelling in joints, other than neck, back or hips, level of discomfort from any areas tender to touch or pressure, and level of morning stiffness), the response is from 0 (none) to 10 (very severe); for Question 6 (duration of morning stiffness), the response is from 0 (0 hours) to 10 (≥ 2 hours). The overall BASDAI score ranges from 0 to 10. Lower scores indicate less disease activity.
A BASDAI 50 response is defined as improvement of 50% or more from Baseline in BASDAI score. Participants with missing data or who discontinued study drug prior to Week 14 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[13]	93[14]		
Units: percentage of participants				
number (confidence interval 95%)	23.4 (14.8 to 32.0)	45.2 (35.0 to 55.3)		

Notes:

[13] - Full analysis set

[14] - Full analysis set

Statistical analyses

Statistical analysis title	Analyis of BASDAI 50 Response
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.002 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	35

Notes:

[15] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including BASDAI 50; within the group, the allocated α was adjusted based on the magnitude of p values.

[16] - Cochran-Mantel-Haenszel test adjusting for stratification factor of Screening hsCRP level.

Secondary: Change From Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) Score

End point title	Change From Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) Score

End point description:

The ASQoL consists of 18 items related to quality of life, including the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. Each item is answered as yes (scored as 1) or no (scored as 0).
Scores are summed to obtain the overall score which ranges from 0 to 18, where higher scores indicate a worse quality of life. A negative change from Baseline in ASQoL indicates improvement in quality of life.
A mixed effect model repeat measurement (MMRM) analysis with longitudinal data from observed cases up to Week 14 was used.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[17]	88[18]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-2.67 (-3.58 to -1.75)	-4.20 (-5.12 to -3.29)		

Notes:

[17] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

[18] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in ASQoL Score
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.16 [20]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	-0.3

Notes:

[19] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including ASQoL; within the group, the allocated α was adjusted based on the magnitude of p values.

[20] - MMRM model includes treatment, visit, treatment-by-visit interaction as fixed effects and Screening hsCRP level and Baseline value as covariates.

Secondary: Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) Partial Remission

End point title	Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) Partial Remission

End point description:

ASAS partial remission (PR) is defined as an absolute score of ≤ 2 units on a 0 to 10 scale for each of the four following domains:
1) Patient's global assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (no activity) to 10 (severe activity);
2) Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe pain);
3) Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
4) Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).
Participants with missing data or who discontinued study drug prior to Week 14 were counted as non-responders.

End point type	Secondary

End point timeframe:

Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[21]	93[22]		
Units: percentage of participants				
number (confidence interval 95%)	1.1 (0.0 to 3.1)	19.4 (11.3 to 27.4)		

Notes:

[21] - Full analysis set

[22] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ASAS Partial Remission
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.001 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	26.6

Notes:

[23] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including ASAS PR; within the group, the allocated α was adjusted based on the magnitude of p values.

[24] - Cochran-Mantel-Haenszel test adjusting for stratification factor of Screening hsCRP level.

Secondary: Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14

End point title	Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 14

End point description:

The Bath Ankylosing Spondylitis Functional Index is a validated index to determine the degree of functional limitation in patients with AS. BASFI consists of 10 questions assessing participants' ability to perform activities such as putting on socks, bending, reaching, getting up from the floor or an armless chair, standing, climbing and other physical activities. Each item is scored on a NRS ranging from 0 (easy to perform an activity) to 10 (impossible to perform an activity). The overall score is the mean of the 10 items and ranges from 0 to 10 with higher scores indicating more functional limitations. A negative change from Baseline in BASFI indicates improvement.
A mixed effect model repeat measurement (MMRM) analysis with longitudinal data from observed cases up to Week 14 was used.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[25]	86[26]		
Units: score n a scale				
least squares mean (confidence interval 5%)	-1.30 (-1.74 to -0.86)	-2.29 (-2.73 to -1.85)		

Notes:

[25] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

[26] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in BASFI
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	172
Analysis specification	Post-hoc
Analysis type	superiority[27]
P-value	= 0.001 [28]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.39

Notes:

[27] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including BASFI; within the group, the allocated α was adjusted based on the magnitude of p values.

[28] - MMRM model includes treatment, visit, treatment-by-visit interaction as fixed effects and Screening hsCRP level and Baseline value as covariates.

Secondary: Change From Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMI[Lin]) at Week 14

End point title	Change From Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMI[Lin]) at Week 14

End point description:

The BASMI is a composite score based on 5 direct measurements of spinal mobility:
1) cervical rotation (measured in degrees),
2) tragus to wall distance (in centimeters [cm]),
3) lumbar side flexion (in cm),
4) lumbar flexion (modified Schober's) (in cm), and
5) intermalleolar distance (in cm).
Each measurement is converted to a linear score between 0 and 10. The total BASMI score is the average of the 5 scores and ranges from 0 to 10; the higher the BASMI score the more severe the patient's limitation of movement due to their ankylosing spondylitis. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89[29]	89[30]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.14 (-0.29 to 0.01)	-0.37 (-0.52 to -0.21)		

Notes:

[29] - Full analysis set participants with available data

[30] - Full analysis set participants with available data

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in BASMI(lin)
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.03 [32]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.02

Notes:

[31] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including BASMI(lin); within the group, the allocated α was adjusted based on the magnitude of p values.

[32] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Secondary: Change From Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14

End point title	Change From Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) at Week 14

End point description:

The MASES evaluation was conducted to assess the presence or absence of enthesitis (inflammation of the entheses, or sites where tendons or ligaments insert into the bone) at 13 different sites (first costochondral joint left/right, seventh costochondral joint left/right, posterior superior iliac spine left/right, anterior superior iliac spine left/right, iliac crest left/right, fifth lumbar spinous process, and proximal insertion of Achilles tendon left/right. Each site was scored for presence (1) or absence (0) of enthesitis. The MASES is the sum of the 13 site scores, and ranges from 0 to 13, with higher scores indicating more inflammation of the entheses.
A mixed effect model repeat measurement (MMRM) analysis with longitudinal data from observed cases up to Week 14 was used.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51[33]	50[34]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-1.41 (-2.02 to -0.80)	-2.25 (-2.86 to -1.64)		

Notes:

[33] - Full analysis set participants with Baseline enthesitis; MMRM including all observed data to Week 14

[34] - Full analysis set participants with Baseline enthesitis; MMRM including all observed data to Week 14

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in MASES
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.049 [36]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	0

Notes:

[35] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including MASES; within the group, the allocated α was adjusted based on the magnitude of p values.

[36] - MMRM model includes treatment, visit, treatment-by-visit interaction as fixed effects and Screening hsCRP level and Baseline value as covariates.

Secondary: Change From Baseline in Work Productivity and Activity Impairment (WPAI) Overall Work Impairment at Week 14

End point title	Change From Baseline in Work Productivity and Activity Impairment (WPAI) Overall Work Impairment at Week 14

End point description:

The Work Productivity and Activity Impairment Questionnaire: Axial Spondyloarthritis, Version 2.0 (WPAI-Axial Spondyloarthritis) measures the effect of overall health and specific symptoms on productivity at work and outside of work. It consists of 6 questions. Respondents were asked about time missed from work and time while at work during which productivity was impaired in the past seven days. Results of WPAI are expressed as a percentage of impairment from 0 to 100, with higher percentages indicating greater impairment and less productivity. Overall Work Impairment indicates the percentage of overall work impairment due to health problems. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[37]	55[38]		
Units: percent impairment				
least squares mean (confidence interval 95%)	-12.60 (-19.04 to -6.15)	-18.11 (-24.73 to -11.50)		

Notes:

[37] - Full analysis participants who were employed and with available data

[38] - Full analysis participants who were employed and with available data

Statistical analyses

Statistical analysis title	Analysis of Change in WPAI Overall Work Impairment
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.19 [40]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.82
upper limit	2.78

Notes:

[39] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint. The testing sequence included a group of endpoints tested by the Hochberg procedure, including WPAI; within the group, the allocated α was adjusted based on the magnitude of p values.

[40] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Secondary: Change From Baseline in ASAS Health Index (HI) at Week 14

End point title	Change From Baseline in ASAS Health Index (HI) at Week 14

End point description:

The ASAS HI measures functioning and health across 17 aspects of health in patients with AS, including pain, emotional functions, sleep, sexual function, mobility, self care, and community life. Each of the 17 questions is answered by the participant as "I agree" (score = 1) or "I disagree" (score = 0). The responses to the 17 dichotomous items are summed up to give a total score ranging from 0 to 17, where a higher score indicates a worse health status. A negative change from Baseline indicates improvement.

A mixed effect model repeat measurement (MMRM) analysis with longitudinal data from observed cases up to Week 14 was used.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[41]	88[42]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-1.38 (-2.11 to -0.65)	-2.75 (-3.48 to -2.02)		

Notes:

[41] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

[42] - Full analysis set; MMRM including all observed longitudinal data up to Week 14

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in ASAS HI
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.007 [44]
Method	Mixed Effect Model Repeated Measurement
Parameter estimate	LS Mean Difference
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.37
upper limit	-0.37

Notes:

[43] - To preserve the overall type I error rate at α=0.05 level, a step-down approach was used to test the primary and multiplicity-controlled key secondary endpoints. The testing began with the primary endpoint at α=0.05 and continued conditional on significance of higher-ranked endpoint.
ASAS HI was to be evaluated only if the group of endpoints tested by Hochberg procedure were all significant.

[44] - MMRM model includes treatment, visit, treatment-by-visit interaction as fixed effects and Screening hsCRP level and Baseline value as covariates.

Secondary: Percentage of Participants Achieving an ASAS 20 Response at Week 14

End point title	Percentage of Participants Achieving an ASAS 20 Response at Week 14

End point description:

ASAS 20 response was defined as improvement of ≥ 20% and an absolute improvement of ≥ 1 unit from Baseline in ≥ 3 of the following 4 domains, with no deterioration (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 units [on a scale of 0 to 10]) in the remaining domain:
1) Patient's global assessment of disease activity, measured on a NRS from 0 - 10 (severe activity);
2) Pain, measured by the total back pain NRS from 0 - 10 (most severe pain);
3) Function, measured by the BASFI, consisting of 10 items assessing participants' ability to perform activities each on an NRS from 0 (easy) - 10 (impossible);
4) Inflammation, measured by the mean of the 2 morning stiffness-related BASDAI NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/≥ 2 hours duration).
Participants with missing data or who discontinued study drug prior to Week 14 were counted as non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[45]	93[46]		
Units: percentage of participants				
number (confidence interval 95%)	40.4 (30.5 to 50.3)	64.5 (54.8 to 74.2)		

Notes:

[45] - Full analysis set

[46] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ASAS 20 Response
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.001 [48]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.2
upper limit	38

Notes:

[47] - This comparison was not part of the pre-specified multiplicity testing sequence.

[48] - Cochran-Mantel-Haenszel test adjusting for stratification factor of Screening hsCRP level.

Secondary: Change From Baseline in SPARCC MRI Score for Sacroiliac Joints at Week 14

End point title	Change From Baseline in SPARCC MRI Score for Sacroiliac Joints at Week 14

End point description:

In the SPARCC MRI assessment of the sacroiliac (SI) joints 6 consecutive sacroiliac joint image coronal slices representing the largest proportion of the synovial compartment of the SI joints were assessed for edema, intensity and depth of edema.
Each SI joint (left and right) was divided into quadrants for a total of 8 SI scoring locations. Each quadrant was scored for the presence (1) or absence (0) of edema, intensity of edema (a score of 1 was assigned for each SI joint (left and right) if an intense signal was seen in any quadrant of that joint for each slice), and a lesion was graded as deep (score of 1) if there was homogeneous and unequivocal increase in signal extending over a depth of at least 1 cm from the articular surface of the SI joint in any quadrant.
The total maximum score for all SI joints across 6 slices is 72.
MRI data up to 3 days post first dose (for Baseline) and up to first dose of period 2 for Week 14 were included in the anlaysis.

End point type	Secondary

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[49]	68[50]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.22 (-1.47 to 1.04)	-3.91 (-5.05 to -2.77)		

Notes:

[49] - Full analysis set with available MRI data during pre-specified time window

[50] - Full analysis set with available MRI data during pre-specified time window

Statistical analyses

Statistical analysis title	Analysis of Change in SPARCC MRI SI Joint Score
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	< 0.001 [52]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.31
upper limit	-2.08

Notes:

[51] - This comparison was not part of the pre-specified multiplicity testing sequence.

[52] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Post-hoc: Change From Baseline in SPARCC MRI Score for the Spine at Week 14 - Supplementary Analysis

End point title	Change From Baseline in SPARCC MRI Score for the Spine at Week 14 - Supplementary Analysis

End point description:

The entire spine was evaluated for active inflammation (bone marrow edema). Six DVUs representing the most abnormal DVUs were selected to calculate the SPARCC MRI spine score. For each DVU, 3 consecutive sagittal slices were assessed in 4 quadrants to evaluate the extent of inflammation in all dimensions. Each quadrant was scored for the presence (1) or absence (0) of edema. If edema was present in at least 1 quadrant of a DVU slice, it was also scored for intensity and depth of the edema representing that slice: An additional score of 1 was assigned if an intense signal was seen in any quadrant on a DVU slice. Slices that included a lesion demonstrating continuous increased signal of depth ≥ 1 cm extending from the endplate were scored as an additional 1 per slice. The maximum (worst) overall score for all 6 DVUs is 108.
A supplemental post-hoc SPARCC MRI analysis included all MRI data collected at nominal visits at Baseline and Week 14.

End point type	Post-hoc

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88[53]	89[54]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.65 (-2.20 to 0.90)	-6.86 (-8.41 to -5.30)		

Notes:

[53] - Full analysis set participants with available MRI data at Baseline and Week 14

[54] - Full analysis set participants with available MRI data at Baseline and Week 14

Statistical analyses

Statistical analysis title	Supplementary Analysis of SPARCC MRI Spine Score
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	177
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.001 [55]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-6.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.27
upper limit	-4.14

Notes:

[55] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Post-hoc: Change From Baseline in SPARCC MRI Score for Sacroiliac Joints at Week 14 - Supplementary Analysis

End point title	Change From Baseline in SPARCC MRI Score for Sacroiliac Joints at Week 14 - Supplementary Analysis

End point description:

In the SPARCC MRI assessment of the sacroiliac joints 6 consecutive sacroiliac joint image coronal slices representing the largest proportion of the synovial compartment of the SI joints were assessed for edema, intensity and depth of edema.
Each SI joint (left and right) was divided into quadrants for a total of 8 SI scoring locations. Each quadrant was scored for the presence (1) or absence (0) of edema, intensity of edema (a score of 1 was assigned for each SI joint (left and right) if an intense signal was seen in any quadrant of that joint for each slice), and a lesion was graded as deep (score of 1) if there was homogeneous and unequivocal increase in signal extending over a depth of at least 1 cm from the articular surface of the SI joint in any quadrant. The total maximum score for all SI joints across 6 slices is 72.
A supplemental post-hoc SPARCC MRI analysis was done to include all MRI data collected at nominal visits at Baseline and Week 14.

End point type	Post-hoc

End point timeframe:

Baseline and Week 14

End point values	Placebo	Upadacitinib 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[56]	89[57]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.90 (-2.01 to 0.20)	-3.45 (-4.54 to -2.36)		

Notes:

[56] - Full analysis set participants with available MRI data at Baseline and Week 14

[57] - Full analysis set participants with available MRI data at Baseline and Week 14

Statistical analyses

Statistical analysis title	Supplmentary Analysis of SPARCC MRI SI Joint Score
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	176
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.001 [58]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	-1.08

Notes:

[58] - ANCOVA model including treatment and Screening hsCRP level as fixed factors and Baseline value as covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1: From the first dose of study drug to Week 14.
Period 1+2: Week 14 to 30 days after last dose (94 weeks) for subjects initially assigned to placebo; Week 1 to 30 days after last dose (108 weeks) for subjects initially assigned to upadacitinib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Period 1: Placebo

Reporting group description:

Participants received matching placebo orally once a day for 14 weeks in Period 1.

Reporting group title	Period 1: Upadacitinib 15 mg

Reporting group description:

Participants received 15 mg upadacitinib orally once a day for 14 weeks in Period 1.

Reporting group title	Period 1+2: Upadacitinib 15 mg

Reporting group description:

Participants originally assigned to placebo received upadacitinib 15 mg from Week 14 to Week 104.
Participants originally assigned to upadacitinib received upadacitinib 15 mg from Week 0 to Week 104.

Serious adverse events	Period 1: Placebo	Period 1: Upadacitinib 15 mg	Period 1+2: Upadacitinib 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 94 (1.06%)	1 / 93 (1.08%)	16 / 182 (8.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SQUAMOUS CELL CARCINOMA OF THE TONGUE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

ANKLE FRACTURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
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 FRACTURES			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC DILATATION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE EMERGENCY			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
CARDIOVASCULAR DISORDER			
subjects affected / exposed	1 / 94 (1.06%)	0 / 93 (0.00%)	0 / 182 (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

Nervous system disorders			
HEMIPARAESTHESIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO POSITIONAL			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
APPENDICITIS NONINFECTIVE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE PROLAPSE			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			

subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
BLISTER			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEOARTHRITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIARTHRITIS			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	0 / 94 (0.00%)	1 / 93 (1.08%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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	Period 1: Placebo	Period 1: Upadacitinib 15 mg	Period 1+2: Upadacitinib 15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 94 (22.34%)	26 / 93 (27.96%)	104 / 182 (57.14%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 94 (2.13%)	5 / 93 (5.38%)	13 / 182 (7.14%)
occurrences (all)	2	5	14
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	2 / 94 (2.13%)	8 / 93 (8.60%)	29 / 182 (15.93%)
occurrences (all)	2	8	35
Nervous system disorders			
HEADACHE			
subjects affected / exposed	2 / 94 (2.13%)	5 / 93 (5.38%)	15 / 182 (8.24%)
occurrences (all)	2	5	16
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	5 / 94 (5.32%)	5 / 93 (5.38%)	13 / 182 (7.14%)
occurrences (all)	5	5	14
NAUSEA			
subjects affected / exposed	5 / 94 (5.32%)	1 / 93 (1.08%)	6 / 182 (3.30%)
occurrences (all)	5	1	6
Musculoskeletal and connective tissue disorders			
ANKYLOSING SPONDYLITIS			
subjects affected / exposed	4 / 94 (4.26%)	0 / 93 (0.00%)	13 / 182 (7.14%)
occurrences (all)	4	0	20
BACK PAIN			
subjects affected / exposed	4 / 94 (4.26%)	1 / 93 (1.08%)	11 / 182 (6.04%)
occurrences (all)	5	1	11
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	4 / 94 (4.26%)	5 / 93 (5.38%)	35 / 182 (19.23%)
occurrences (all)	4	6	48
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 94 (3.19%)	2 / 93 (2.15%)	23 / 182 (12.64%)
occurrences (all)	3	2	30

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2017	•Removed upadacitinib 30 mg QD dose from study plan. •Updated Phase from 2b/3 to Phase 2/3. •Clarified definition of inadequate response to NSAIDs required for enrollment. •Updated number of sites from 120 to 107. •Updated subject enrollment from 228 to 170. •Modified Period 2 study design from blinded to open-label with only one dose (15 mg). •Allowed earlier option of rescue therapy (Week 16 for concomitant pain medications and Week 20 for certain csDMARDs). •Allowed earlier discontinuation of study drug, and assessment of ASAS 20 from Week 16. •Updated results from other clinical trials in benefits and risks. •Updated references to spondyloarthritis to specify axial manifestation. •Removed statement on subject enrollment after target number reached. •Updated tuberculosis testing and prophylaxis information. •Updated schedule for subjects still participating in the study but discontinued study drug. •Updated contraception requirements for females. •Updated purpose and assessment of x-ray, MRI, and low-dose computed tomography. •Updated requirements for local hsCRP testing. •Updated Hepatitis B infection definition and testing requirements. •Clarified the impact of corticosteroid injections on swollen joint and dactylitis assessments. •Added embolic and thrombotic events to the Adverse Events (AE) of Special Interest and added a Supplemental CRF. •Updated safety assessments to reference Common Terminology Criteria. •Updated AE collection for subjects continuing in the study but discontinued study drug. •Updated supplemental information to be collected for certain cardiovascular, herpes zoster, and thrombotic/embolic AEs. •Updated SUSAR reporting reference. •Updated pregnancy information to be collected. •Updated toxicity management guidelines for serum creatinine and creatine phosphokinase and added gastrointestinal perforation. •Updated the timeframe for product complaint reporting. •Updated multiplicity control and statistical power.
20 December 2019	• Added events of deep vein thrombosis (DVT) and pulmonary embolism (PE) to the adverse events that have been observed in subjects who receive JAK inhibitors, including upadacitinib. • Added management of thrombosis events. • Added management of herpes zoster and a recommendation for periodic skin examination for subjects who are at increased risk for skin cancer. • Amended the wording for subjects who experience a study drug interruption > 7 consecutive days during Weeks 1 through 14 (Period 1) or > 30 consecutive days during Period 2 to allow the Investigator to decide if the drug should be re-started; previous wording required that upadacitinib be permanently discontinued if interruptions of those lengths occurred.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported