Clinical trial results:
A Phase 3, Randomized, Double-Blind Study Comparing ABT-494 Monotherapy to Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response to MTX

Summary

EudraCT number	2015-003376-75
Trial protocol	ES GR CZ BE PL HU PT AT BG IT
Global end of trial date	10 August 2022

Results information

Result version number	v1 (current)
This version publication date	06 August 2023
First version publication date	06 August 2023

Trial information

Trial identification

Sponsor protocol code	M15-555

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02706951
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 Ltd, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie Ltd, 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	10 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2017
Global end of trial reached?	Yes
Global end of trial date	10 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To compare the safety and efficacy (signs and symptoms) of ABT-494 monotherapy versus MTX in MTX-inadequate response (MTX-IR) subjects with moderately to severely active rheumatoid arthritis (RA).
• To evaluate the long-term safety, tolerability, and efficacy of ABT-494 in subjects with RA.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 33
Country: Number of subjects enrolled	Chile: 45
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Puerto Rico: 3
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	Serbia: 13
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Ukraine: 31
Country: Number of subjects enrolled	United States: 189
Country: Number of subjects enrolled	Poland: 71
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 15

Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	648
EEA total number of subjects	157

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)	518
From 65 to 84 years	130
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 648 participants with rheumatoid arthritis (RA) on a stable dose of methotrexate (MTX) were randomized at 138 study sites located in 24 countries.

Pre-assignment

Screening details:

Participants were randomized in a 2:2:1:1 ratio to 1 of 4 groups:
Upadacitinib 30 mg (Periods 1 and 2)
Upadacitinib 15 mg (Periods 1 and 2)
MTX (Period 1) upadacitinib 30 mg (Period 2)
MTX (Period 1) upadacitinib 15 mg (Period 2)
Randomization was stratified by geographic region. The MTX groups were pooled for Week 14 analyses.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Period 1: Methotrexate

Arm description:

Participants randomized to receive up to 25 mg methotrexate once a week and placebo to upadacitinib once daily for 14 weeks in Period 1.

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

Dosage and administration details:

Participants randomized to receive up to 25 mg methotrexate once a week and placebo to upadacitinib once daily (QD) for 14 weeks in Period 1.

Arm title	Period 1: Upadacitinib 15 mg

Arm description:

Participants randomized to receive upadacitinib 15 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.

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

Dosage and administration details:

Participants randomized to receive upadacitinib 15 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.

Arm title	Period 1: Upadacitinib 30 mg

Arm description:

Participants randomized to receive upadacitinib 30 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.

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

Dosage and administration details:

Participants randomized to receive upadacitinib 30 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.

Number of subjects in period 1	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Started	216	217	215
Completed	203	201	205
Not completed	13	16	10
Consent withdrawn by subject	10	6	6
Adverse event, non-fatal	1	5	3
Other	2	1	-
Lost to follow-up	-	4	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Upadacitinib 15 mg

Arm description:

Continuing Period 1 participants that were randomized into the upadacitinib 15 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 15 mg once daily in Period 2

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

Dosage and administration details:

Continuing Period 1 participants that were randomized into the upadacitinib 15 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 15 mg once daily in Period 2

Arm title	Upadacitinib 30 mg

Arm description:

Continuing Period 1 participants that were randomized into the upadacitinib 30 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 30 mg once daily in Period 2

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

Dosage and administration details:

Continuing Period 1 participants that were randomized into the upadacitinib 30 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 30 mg once daily in Period 2

Number of subjects in period 2[1]	Upadacitinib 15 mg	Upadacitinib 30 mg
Started	302	300
Completed	184	180
Not completed	118	120
Consent withdrawn by subject	38	44
Adverse event, non-fatal	25	34
Other	37	31
Lost to follow-up	17	9
COVID-19 Related	1	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The participants that were randomized into two of the three arms in Period 1 (Upadacitinib 15 mg & Upadacitinib 20 mg) continued in those arms during Period 2. The remaining participants that were assigned to the Methotrexate arm in Period 1 were then assigned to either Upadacitinib 15 mg & Upadacitinib 20 mg in Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	Period 1: Methotrexate
Reporting group description:	
Participants randomized to receive up to 25 mg methotrexate once a week and placebo to upadacitinib once daily for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 15 mg
Reporting group description:	
Participants randomized to receive upadacitinib 15 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 30 mg
Reporting group description:	
Participants randomized to receive upadacitinib 30 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	

Reporting group values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Number of subjects	216	217	215
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	171	175	172
From 65-84 years	45	42	43
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.3	54.5	53.1
standard deviation	± 11.12	± 12.20	± 12.72
Gender categorical			
Units: Subjects			
Female	179	174	170
Male	37	43	45
Duration of Rheumatoid Arthritis Diagnosis			
Units: Years			
arithmetic mean	5.8	7.5	6.5
standard deviation	± 6.63	± 8.88	± 6.98
Tender Joint Count			
Measure Description: A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: Joints			
arithmetic mean	25.2	24.5	24.8
standard deviation	± 15.99	± 15.10	± 15.19
Swollen Joint Count			

Measure Description: A total of 66 joints were assessed for the presence or absence of swelling.			
Units: Joints			
arithmetic mean	16.9	16.4	16.9
standard deviation	±	± 10.94	± 10.23
Patient's Assessment of Pain			
Measure Description: Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale (VAS) from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	62.5	62.3	61.9
standard deviation	± 21.26	± 22.53	± 22.12
Patient's Global Assessment of Disease Activity			
[1] Measure 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. [2] Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	59.6	62.2	59.4
standard deviation	± 21.78	± 22.29	± 22.79
Physician's Global Assessment of Disease Activity			
Measure Description: The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	62.1	65.7	62.6
standard deviation	± 17.47	± 18.49	± 17.81
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Measure 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			
Units: Units on a Scale			
arithmetic mean	1.5	1.5	1.5
standard deviation	± 0.66	± 0.66	± 0.65
High-sensitivity C- reactive Protein (hsCRP)			
Units: mg/L			
arithmetic mean	14.5	14.0	16.3
standard deviation	± 17.33	± 16.49	± 20.77
Disease Activity Score 28 Based on CRP (DAS28[CRP])			
Measure 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity. A DAS28 score > 5.1 indicates high disease activity, a DAS28 score ≤3.2 indicates low			

disease activity, and a DAS28 score < 2.6 indicates clinical remission.			
Units: Units on a Scale			
arithmetic mean	5.6	5.6	5.6
standard deviation	± 1.04	± 0.92	± 1.06

Reporting group values	Total		
Number of subjects	648		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	518		
From 65-84 years	130		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	523		
Male	125		
Duration of Rheumatoid Arthritis Diagnosis			
Units: Years			
arithmetic mean			
standard deviation	-		
Tender Joint Count			
Measure Description: A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: Joints			
arithmetic mean			
standard deviation	-		
Swollen Joint Count			
Measure Description: A total of 66 joints were assessed for the presence or absence of swelling.			
Units: Joints			
arithmetic mean			
standard deviation	-		
Patient's Assessment of Pain			
Measure Description: Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale (VAS) from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean			
standard deviation	-		

Patient's Global Assessment of Disease Activity			
[1] Measure 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. [2] Measure Analysis Population Description: Participants with available data			
Units: mm arithmetic mean standard deviation	- 		
Physician's Global Assessment of Disease Activity			
Measure Description: The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. Measure Analysis Population Description: Participants with available data			
Units: mm arithmetic mean standard deviation	- 		
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Measure 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			
Units: Units on a Scale arithmetic mean standard deviation	- 		
High-sensitivity C- reactive Protein (hsCRP) Units: mg/L arithmetic mean standard deviation	- 		
Disease Activity Score 28 Based on CRP (DAS28[CRP])			
Measure 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity. A DAS28 score > 5.1 indicates high disease activity, a DAS28 score ≤3.2 indicates low disease activity, and a DAS28 score < 2.6 indicates clinical remission.			
Units: Units on a Scale arithmetic mean standard deviation	- 		

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all randomized participants who received at least 1 dose of study drug.

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	648		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	518		
From 65-84 years	130		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	54.3		
standard deviation	± 12.05		
Gender categorical Units: Subjects			
Female	523		
Male	125		
Duration of Rheumatoid Arthritis Diagnosis Units: Years			
arithmetic mean	6.6		
standard deviation	± 7.58		
Tender Joint Count			
Measure Description: A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: Joints			
arithmetic mean	24.8		
standard deviation	± 15.41		
Swollen Joint Count			
Measure Description: A total of 66 joints were assessed for the presence or absence of swelling.			
Units: Joints			
arithmetic mean	16.7		
standard deviation	± 10.90		
Patient's Assessment of Pain			
Measure Description: Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale (VAS) from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	62.3		
standard deviation	± 21.94		
Patient's Global Assessment of Disease Activity			
[1] Measure 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. [2] Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	60.4		
standard deviation	± 22.29		
Physician's Global Assessment of Disease Activity			
Measure Description: The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. Measure Analysis Population Description: Participants with available data			
Units: mm			
arithmetic mean	63.5		
standard deviation	± 17.98		
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
Measure 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			
Units: Units on a Scale			
arithmetic mean	1.5		
standard deviation	± 0.66		
High-sensitivity C- reactive Protein (hsCRP) Units: mg/L			
arithmetic mean	14.9		
standard deviation	± 18.28		
Disease Activity Score 28 Based on CRP (DAS28[CRP])			
Measure 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity. A DAS28 score > 5.1 indicates high disease activity, a DAS28 score ≤3.2 indicates low disease activity, and a DAS28 score < 2.6 indicates clinical remission.			
Units: Units on a Scale			
arithmetic mean	5.6		
standard deviation	± 1.01		

End points

End points reporting groups

Reporting group title	Period 1: Methotrexate
Reporting group description:	
Participants randomized to receive up to 25 mg methotrexate once a week and placebo to upadacitinib once daily for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 15 mg
Reporting group description:	
Participants randomized to receive upadacitinib 15 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 30 mg
Reporting group description:	
Participants randomized to receive upadacitinib 30 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	
Reporting group title	Upadacitinib 15 mg
Reporting group description:	
Continuing Period 1 participants that were randomized into the upadacitinib 15 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 15 mg once daily in Period 2	
Reporting group title	Upadacitinib 30 mg
Reporting group description:	
Continuing Period 1 participants that were randomized into the upadacitinib 30 mg once daily arm combined with Period 1 Methotrexate (MTX) participants that were randomized to receive upadacitinib 30 mg once daily in Period 2	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) included all randomized participants who received at least 1 dose of study drug.	

Primary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 14

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 14
End point description:	
The primary endpoint for United States (US)/Food and Drug Administration (FDA) regulatory purposes was ACR 20% response (ACR20) at Week 14. 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 and week 14	

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	217	215	
Units: percentage of participants				
number (confidence interval 95%)				
Percentage of Participants With an ACR20 Response	41.2 (34.6 to 47.8)	67.7 (61.5 to 74.0)	71.2 (65.1 to 77.2)	

Statistical analyses

Statistical analysis title	Percentage of Participants With an ACR20 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	26.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.5
upper limit	35.6

Notes:

[1] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[2] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05

Statistical analysis title	Percentage of Participants With an ACR20 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	30

Confidence interval	
level	95 %
sides	2-sided
lower limit	21
upper limit	38.9

Notes:

[3] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.
[4] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Primary: Percentage of Participants Achieving LDA Based on DAS28(CRP) at Week 14

End point title	Percentage of Participants Achieving LDA Based on DAS28(CRP) at Week 14

End point description:

The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes was low
disease activity, based on a Disease Activity Score 28 (DAS28)-CRP score of ≤3.2 at Week 14.
The DAS28 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where
higher scores indicate more disease activity.
A DAS28 score less than or equal to 3.2 indicates low disease activity.

End point type	Primary

End point timeframe:

Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	217	215	
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants Achieving LDA	19.4 (14.2 to 24.7)	44.7 (38.1 to 51.3)	53.0 (46.4 to 59.7)	

Statistical analyses

Statistical analysis title	Percentage of Participants Achieving LDA

Statistical analysis description:

Statistical Analysis 1 for Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg

Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	25.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.8
upper limit	33.7

Notes:

[5] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[6] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Percentage of Participants Achieving LDA

Statistical analysis description:

Statistical Analysis 1 for Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	33.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.1
upper limit	42.1

Notes:

[7] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[8] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Change From Baseline in Disease Activity Score 28 (CRP) at Week 14

End point title	Change From Baseline in Disease Activity Score 28 (CRP) at Week 14

End point description:

The DAS28 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 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 to Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	215	215	213	
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-1.20 (-1.20 to -1.01)	-2.29 (-2.48 to -2.10)	-2.61 (-2.80 to -2.41)	

Statistical analyses

Statistical analysis title	Change From Baseline in CRP at Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.85

Notes:

[9] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Change From Baseline in CRP at Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg

Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.64
upper limit	-1.17

Notes:

[10] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Change From Baseline in Heath Assessment Questionnaire and Disability Index (HAQ-DI) at Week 14

End point title	Change From Baseline in Heath Assessment Questionnaire and Disability Index (HAQ-DI) at Week 14

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. A negative change from Baseline in the overall score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	216	215	
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-0.32 (-0.41 to -0.23)	-0.65 (-0.73 to -0.56)	-0.73 (-0.82 to -0.64)	

Statistical analyses

Statistical analysis title	Change From Baseline in HAQ-DI at Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.22

Notes:

[11] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Change From Baseline in HAQ-DI at Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.3

Notes:

[12] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Change From Baseline in Short-Form 36 (SF-36) Physical Component Score (PCS) at Week 14

End point title	Change From Baseline in Short-Form 36 (SF-36) Physical Component Score (PCS) at Week 14

End point description:

The Short Form 36-Item Health Survey (SF-36) Version 2 is a self-administered questionnaire that measures the impact of disease on overall quality of life during the past 4 weeks. The SF-36 consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health).
The physical component score is a weighted combination of the 8 subscales with positive weighting for physical functioning, role-physical, bodily pain, and general health. The PCS was calculated using norm-based scoring so that 50 is the average score and the standard deviation equals 10. Higher scores are associated with better functioning/ quality of life; a positive change from baseline score indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	195	200	201	
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	4.32 (3.19 to 5.44)	8.28 (7.17 to 9.40)	10.19 (9.07 to 11.30)	

Statistical analyses

Statistical analysis title	Change From Baseline in SF-36 PCS at Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	3.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.52
upper limit	5.42

Notes:

[13] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Change From Baseline in SF-36 PCS Week 14

Statistical analysis description:

The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	5.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.42
upper limit	7.32

Notes:

[14] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 14

End point title	Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 14

End point description:

The DAS28 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 (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity.
A DAS28 score less than 2.6 indicates clinical remission.

End point type	Secondary

End point timeframe:

Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	217	215	
Units: Percentage of Participants				
number (confidence interval 95%)	8.3 (4.6 to 12.0)	28.1 (22.1 to 34.1)	40.5 (33.9 to 47.0)	

Statistical analyses

Statistical analysis title	Percentage of Participants Achieving CR CRP

Statistical analysis description:

Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg

Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.8
upper limit	26.8

Notes:

[15] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[16] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Percentage of Participants Achieving CR CRP

Statistical analysis description:

Percentage of Participants Achieving Clinical Remission (CR) Based on DAS28(CRP) at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	32.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.6
upper limit	39.7

Notes:

[17] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[18] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Change From Baseline in Duration of Morning Stiffness at Week 14

End point title	Change From Baseline in Duration of Morning Stiffness at Week 14

End point description:

Participants were asked to indicate the time it took for them to get as limber as possible after awakening with morning stiffness over the past 7 days. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	196	199	202	
Units: Minutes				
least squares mean (confidence interval 95%)	-53.03 (-72.18 to -33.88)	-94.56 (-113.57 to -75.54)	-102.34 (-121.24 to -83.45)	

Statistical analyses

Statistical analysis title	Change From Baseline in Duration of Morning Stiffn

Statistical analysis description:

Change From Baseline in Duration of Morning Stiffness at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.001 [20]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-41.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-66.56
upper limit	-16.5

Notes:

[19] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[20] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Statistical analysis title	Change From Baseline in Duration of Morning Stiffn

Statistical analysis description:

Change From Baseline in Duration of Morning Stiffness at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.001 [22]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-49.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.23
upper limit	-24.4

Notes:

[21] - The overall type I error prevalence of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled by means of a graphic multiple testing procedure.

[22] - The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

Secondary: Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 14

End point title	Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 14

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	Secondary

End point timeframe:

Baseline and Week 14

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	217	215	
Units: Percentage of Participants				
number (confidence interval 95%)	15.3 (10.5 to 20.1)	41.9 (35.4 to 48.5)	52.1 (45.4 to 58.8)	

Statistical analyses

Statistical analysis title	Percentage of Participants With an ACR50 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	26.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.5
upper limit	34.8

Notes:

[23] - This comparison was not part of the pre-specified multiplicity testing sequence; the nominal p-value is reported.

Statistical analysis title	Percentage of Participants With an ACR50 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	36.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.6
upper limit	45

Notes:

[24] - This comparison was not part of the pre-specified multiplicity testing sequence; the nominal p-value is reported.

Secondary: Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 14

End point title	Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 14

End point description:

Participants who met the following 3 conditions for improvement from baseline were classified as meeting the ACR50
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	Secondary
End point timeframe:	
Baseline and Week 14	

End point values	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	216	217	215	
Units: Percentage of Participants				
number (confidence interval 95%)	2.8 (0.6 to 5.0)	22.6 (17.0 to 28.1)	33.0 (26.7 to 39.3)	

Statistical analyses

Statistical analysis title	Percentage of Participants With an ACR70 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 15 mg
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [25]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.8
upper limit	25.8

Notes:

[25] - This comparison was not part of the pre-specified multiplicity testing sequence; the nominal p-value is reported.

Statistical analysis title	Percentage of Participants With an ACR70 Response

Statistical analysis description:

Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 14

Comparison groups	Period 1: Methotrexate v Period 1: Upadacitinib 30 mg

Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [26]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.6
upper limit	36.9

Notes:

[26] - This comparison was not part of the pre-specified multiplicity testing sequence; the nominal p-value is reported.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 5 years from baseline	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Period 1: Methotrexate
Reporting group description: Participants randomized to receive up to 25 mg methotrexate once a week and placebo to upadacitinib once daily for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 15 mg
Reporting group description: Participants randomized to receive upadacitinib 15 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	
Reporting group title	Period 1: Upadacitinib 30 mg
Reporting group description: Participants randomized to receive upadacitinib 30 mg once daily and placebo to methotrexate once a week for 14 weeks in Period 1.	
Reporting group title	Period 2: Upadacitinib 15 mg
Reporting group description: Participants randomized to receive upadacitinib 15 mg once daily	
Reporting group title	Period 2: Upadacitinib 30 mg
Reporting group description: Participants randomized to receive upadacitinib 30 mg once daily	
Reporting group title	Period 2: Upadacitinib 15 mg Switched From Upadacitinib 30 mg
Reporting group description: Starting with Amendment 5, all participants will receive open-label upadacitinib 15 mg once daily, including those currently on upadacitinib 30 mg once daily	

Serious adverse events	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 216 (3.24%)	11 / 217 (5.07%)	6 / 215 (2.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Spondylolisthesis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Basal cell carcinoma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign lung neoplasm			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Colon adenoma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paget's disease of nipple			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Hypertensive crisis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial vein thrombosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 216 (0.46%)	0 / 217 (0.00%)	0 / 215 (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
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
General physical health deterioration			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Sudden cardiac death			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sudden death			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis chronic			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Dyspnoea			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Device loosening			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device issue			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device loosening			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal injury			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 216 (0.46%)	1 / 217 (0.46%)	0 / 215 (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
Atrial flutter			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paroxysmal atrioventricular block			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow oedema			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed deafness			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Macular hole			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 216 (0.93%)	0 / 217 (0.00%)	0 / 215 (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
Cholecystitis chronic			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis noninfective			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	1 / 216 (0.46%)	0 / 217 (0.00%)	0 / 215 (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
Nephropathy toxic			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 216 (0.46%)	0 / 217 (0.00%)	0 / 215 (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
Osteoarthritis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scoliosis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Appendicitis perforated			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin's abscess			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal osteomyelitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 217 (0.00%)	0 / 215 (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
Tibia fracture			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 2: Upadacitinib 15 mg	Period 2: Upadacitinib 30 mg	Period 2: Upadacitinib 15 mg Switched From Upadacitinib 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 318 (29.87%)	75 / 311 (24.12%)	22 / 205 (10.73%)
number of deaths (all causes)	7	5	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Spondylolisthesis			
subjects affected / exposed	0 / 318 (0.00%)	2 / 311 (0.64%)	0 / 205 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign lung neoplasm			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Bladder cancer			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Breast cancer			
subjects affected / exposed	2 / 318 (0.63%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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 ductal breast carcinoma			
subjects affected / exposed	2 / 318 (0.63%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 318 (0.00%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paget's disease of nipple			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Parathyroid tumour benign			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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 disorders			
Aortic stenosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 318 (0.63%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Hypotension			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Peripheral artery aneurysm			

subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Peripheral artery thrombosis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Superficial vein thrombosis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 318 (0.63%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	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 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
General physical health deterioration			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Impaired healing			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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 organ dysfunction syndrome			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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-cardiac chest pain			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Sudden cardiac death			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 318 (0.63%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Asthma			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Bronchitis chronic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 318 (0.31%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Hydrothorax			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Interstitial lung disease			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Obstructive airways disorder			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Pleurisy			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Pneumothorax			

subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Pulmonary embolism			
subjects affected / exposed	3 / 318 (0.94%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	2 / 205 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Device loosening			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Mental status changes			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Device issue			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Device loosening			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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			
Chest injury			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Fibula fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Foot fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal injury			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Humerus fracture			
subjects affected / exposed	0 / 318 (0.00%)	4 / 311 (1.29%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Ligament rupture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Meniscus injury			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Periprosthetic fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Pneumothorax traumatic			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Rib fracture			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Road traffic accident			
subjects affected / exposed	2 / 318 (0.63%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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 fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Tendon rupture			

subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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			
Angina pectoris			
subjects affected / exposed	1 / 318 (0.31%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	5 / 318 (1.57%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Atrioventricular block first degree			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Atrioventricular block second degree			

subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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 arrest			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	3 / 318 (0.94%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 318 (0.00%)	4 / 311 (1.29%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Palpitations			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Paroxysmal atrioventricular block			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Sinus tachycardia			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 318 (0.31%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intensive care unit acquired weakness			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Intracranial aneurysm			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Ischaemic stroke			
subjects affected / exposed	0 / 318 (0.00%)	2 / 311 (0.64%)	0 / 205 (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
Lacunar stroke			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Sciatica			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Transient global amnesia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Bone marrow oedema			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Iron deficiency anaemia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Lymphadenitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Neutropenia			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Normocytic anaemia			

subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Mixed deafness			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Vertigo			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	3 / 318 (0.94%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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

Diarrhoea			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Diverticulum intestinal			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Oesophagitis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 318 (0.63%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Cholecystitis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Cholecystitis acute			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Cholelithiasis			
subjects affected / exposed	1 / 318 (0.31%)	2 / 311 (0.64%)	0 / 205 (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
Hepatitis acute			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Hepatotoxicity			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 318 (0.00%)	2 / 311 (0.64%)	0 / 205 (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
Cystitis noninfective			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Nephrolithiasis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Nephropathy toxic			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Pelvi-ureteric obstruction			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Renal impairment			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Arthritis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Osteoarthritis			
subjects affected / exposed	5 / 318 (1.57%)	3 / 311 (0.96%)	2 / 205 (0.98%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	2 / 318 (0.63%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Osteoporotic fracture			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Rheumatoid arthritis			
subjects affected / exposed	3 / 318 (0.94%)	5 / 311 (1.61%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Scoliosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Spinal stenosis			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Spondylolisthesis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Arthritis bacterial			
subjects affected / exposed	2 / 318 (0.63%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin's abscess			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Bronchiolitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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	4 / 318 (1.26%)	2 / 311 (0.64%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	2 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 318 (0.31%)	3 / 311 (0.96%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	3 / 318 (0.94%)	0 / 311 (0.00%)	2 / 205 (0.98%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19 pneumonia			

subjects affected / exposed	8 / 318 (2.52%)	4 / 311 (1.29%)	7 / 205 (3.41%)
occurrences causally related to treatment / all	1 / 8	0 / 4	1 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gangrene			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Gastroenteritis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Helicobacter gastritis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Herpes zoster			
subjects affected / exposed	0 / 318 (0.00%)	3 / 311 (0.96%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Oral herpes			

subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Osteomyelitis			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Pneumonia			
subjects affected / exposed	12 / 318 (3.77%)	4 / 311 (1.29%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	8 / 12	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Pyelonephritis			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Pyelonephritis chronic			
subjects affected / exposed	1 / 318 (0.31%)	0 / 311 (0.00%)	0 / 205 (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
Sepsis			
subjects affected / exposed	2 / 318 (0.63%)	2 / 311 (0.64%)	1 / 205 (0.49%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis syndrome			
subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Staphylococcal osteomyelitis			

subjects affected / exposed	0 / 318 (0.00%)	1 / 311 (0.32%)	0 / 205 (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
Urinary tract infection			
subjects affected / exposed	1 / 318 (0.31%)	3 / 311 (0.96%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 318 (0.00%)	0 / 311 (0.00%)	0 / 205 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 318 (0.31%)	1 / 311 (0.32%)	0 / 205 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 318 (0.63%)	0 / 311 (0.00%)	0 / 205 (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

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

Non-serious adverse events	Period 1: Methotrexate	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 216 (22.69%)	43 / 217 (19.82%)	51 / 215 (23.72%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 216 (1.39%)	3 / 217 (1.38%)	5 / 215 (2.33%)
occurrences (all)	4	3	5
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 216 (1.39%)	1 / 217 (0.46%)	1 / 215 (0.47%)
occurrences (all)	3	1	1
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 216 (0.00%)	5 / 217 (2.30%)	9 / 215 (4.19%)
occurrences (all)	0	5	9
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 216 (1.85%)	5 / 217 (2.30%)	0 / 215 (0.00%)
occurrences (all)	4	5	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 216 (0.93%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 217 (0.46%)	3 / 215 (1.40%)
occurrences (all)	0	1	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 216 (1.85%)	2 / 217 (0.92%)	4 / 215 (1.86%)
occurrences (all)	5	2	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 217 (0.00%)	3 / 215 (1.40%)
occurrences (all)	1	0	3
Rheumatoid arthritis			
subjects affected / exposed	10 / 216 (4.63%)	1 / 217 (0.46%)	5 / 215 (2.33%)
occurrences (all)	11	1	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 216 (3.24%)	4 / 217 (1.84%)	4 / 215 (1.86%)
occurrences (all)	7	4	4
COVID-19			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	1 / 216 (0.46%)	3 / 217 (1.38%)	5 / 215 (2.33%)
occurrences (all)	1	3	5
Influenza			

subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences (all)	0	0	0
Latent tuberculosis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 217 (0.00%)	0 / 215 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	7 / 216 (3.24%)	4 / 217 (1.84%)	4 / 215 (1.86%)
occurrences (all)	7	4	5
Upper respiratory tract infection			
subjects affected / exposed	13 / 216 (6.02%)	9 / 217 (4.15%)	6 / 215 (2.79%)
occurrences (all)	16	9	6
Urinary tract infection			
subjects affected / exposed	5 / 216 (2.31%)	10 / 217 (4.61%)	10 / 215 (4.65%)
occurrences (all)	5	11	12

Non-serious adverse events	Period 2: Upadacitinib 15 mg	Period 2: Upadacitinib 30 mg	Period 2: Upadacitinib 15 mg Switched From Upadacitinib 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	219 / 318 (68.87%)	211 / 311 (67.85%)	82 / 205 (40.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 318 (5.35%)	23 / 311 (7.40%)	3 / 205 (1.46%)
occurrences (all)	27	34	3
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 318 (3.46%)	19 / 311 (6.11%)	2 / 205 (0.98%)
occurrences (all)	15	29	2
Blood creatine phosphokinase increased			
subjects affected / exposed	32 / 318 (10.06%)	58 / 311 (18.65%)	7 / 205 (3.41%)
occurrences (all)	57	81	7
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 318 (8.81%)	25 / 311 (8.04%)	6 / 205 (2.93%)
occurrences (all)	30	26	6
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	20 / 318 (6.29%)	18 / 311 (5.79%)	7 / 205 (3.41%)
occurrences (all)	27	20	7
Neutropenia			
subjects affected / exposed	9 / 318 (2.83%)	18 / 311 (5.79%)	3 / 205 (1.46%)
occurrences (all)	17	27	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 318 (2.52%)	20 / 311 (6.43%)	1 / 205 (0.49%)
occurrences (all)	10	24	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 318 (5.66%)	20 / 311 (6.43%)	5 / 205 (2.44%)
occurrences (all)	19	23	5
Rheumatoid arthritis			
subjects affected / exposed	45 / 318 (14.15%)	29 / 311 (9.32%)	9 / 205 (4.39%)
occurrences (all)	60	39	11
Infections and infestations			
Bronchitis			
subjects affected / exposed	39 / 318 (12.26%)	40 / 311 (12.86%)	5 / 205 (2.44%)
occurrences (all)	50	45	5
COVID-19			
subjects affected / exposed	21 / 318 (6.60%)	2 / 311 (0.64%)	20 / 205 (9.76%)
occurrences (all)	21	2	20
Herpes zoster			
subjects affected / exposed	32 / 318 (10.06%)	32 / 311 (10.29%)	6 / 205 (2.93%)
occurrences (all)	33	35	6
Influenza			
subjects affected / exposed	15 / 318 (4.72%)	18 / 311 (5.79%)	2 / 205 (0.98%)
occurrences (all)	15	19	2
Latent tuberculosis			
subjects affected / exposed	25 / 318 (7.86%)	16 / 311 (5.14%)	5 / 205 (2.44%)
occurrences (all)	25	16	5
Nasopharyngitis			
subjects affected / exposed	56 / 318 (17.61%)	38 / 311 (12.22%)	7 / 205 (3.41%)
occurrences (all)	79	65	8

Upper respiratory tract infection			
subjects affected / exposed	38 / 318 (11.95%)	46 / 311 (14.79%)	5 / 205 (2.44%)
occurrences (all)	64	66	5
Urinary tract infection			
subjects affected / exposed	43 / 318 (13.52%)	47 / 311 (15.11%)	13 / 205 (6.34%)
occurrences (all)	69	87	17

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2016	Updated the study design and plan to change the duration of Period 1 from to 14 weeks and added a blinded long term extension (Period 2). Added a 15 mg treatment group. Increased the number of study centers and number of subjects to be enrolled. Described how the blind will be maintained. Added discontinuation procedures. Updated procedures for laboratory samples during the screening period and defined screen failure. Added follow-up procedures. Updated MTX therapy and hsCRP value requirements at Screening. Identified patient questionnaires to be completed. Added international normalized ratio reflex, follicle stimulating hormone, and varicella zoster virus specific immunoglobulin G to clinical chemistry lab tests. Added requirement that a positive result for Hepatitis B surface antibody requires Hepatitis B virus DNA polymerase chain reaction (PCR) testing (for subjects in Japan only). Added testing for varicella zoster virus (for subjects in Japan only). Updated randomization and randomization stratification. Added language regarding the Week 14 interim analysis. Added text to describe the addition of an external DMC. Updated the AST or ALT specific toxicity management guidelines. Added the following exclusion criteria: females who are considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug; male subject who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug; subjects with a history of gastrointestinal (GI) perforation or a history of associated GI diseases; subjects with conditions that could interfere with drug absorption; subjects who have been the recipient of an organ transplant; subjects who had clinically relevant or significant ECG abnormalities; subjects with a positive result of beta-D-glucan (for subjects in Japan only).
29 February 2016	Removed all country-specific language for Japan. Updated RA classification criteria serum pregnancy testing requirements. Added criteria for adjusting or adding background medication at Week 26 if subjects do not achieve LDA as defined by CDAI. ● Amendment 2.01 (Japan only) (09 March 2016, 27 subjects) Added Japan-specific inclusion and exclusion criteria. Updated text to reflect revisions implemented with global protocol Amendment 2 (29 February 2016). ● Amendment 2.02 (VHP countries) (27 May 2016, 128 subjects) Revised to require compliance to local label with the concomitant use of MTX.
06 October 2016	Updated exclusion criteria to reflect normal reference range in the elderly population and the lack of corrected QT interval prolongation with upadacitinib. Added text to follow MTX local label for concomitant treatment contraindications. ● Amendment 3.01 (Japan only) (02 November 2016, 38 subjects) Updated text to reflect revisions implemented with global protocol Amendment 3 (06 October 2016). ● Amendment 3.02 (VHP countries) (04 January 2017, 6 subjects) Updated text to reflect revisions implemented with global protocol Amendment 3 (06 October 2016).

25 October 2017	Removed all references to China throughout the document Added Cebicistat, Troleandomycin, and Rifapentine, and removed Avasimibe from examples of commonly used strong CPY3A inhibitors and inducers. Revised study procedures to prevent unnecessary initiation of tuberculosis (TB) prophylaxis, include Rifapentine as excluded medication for TB, and prevent unnecessary pregnancy testing. Updated text for ranked secondary endpoints, other key secondary endpoints, and additional endpoints to align with SAP. Updated the adverse events of special interest (AESIs) that will be monitored during the study to align in content and presentation with the current version of the Product Safety SAP. Updated definition for assessing the relationship of AEs to use of study drug per sponsor guidelines. Implemented a supplemental eCRF for thrombotic events. Removed last observation carried forward analysis of primary efficacy variable to align with the SAP. Clarified that severity grading of abnormal lab data will be based on Outcome Measures in Rheumatology (OMERACT) criteria or National Cancer Institute (NCI) Common Terminology Criteria (CTC). • Amendment 4.01 (Japan only) (15 November 2017, 0 subjects) Updated text to reflect revisions implemented with global protocol Amendment 4 (25 October 2017). Added guidance for local Hepatitis B virus DNA PCR testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported