



Clinical trial results:

A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo on Stable Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) in Subjects with Moderately to Severely Active Rheumatoid Arthritis with Inadequate Response or Intolerance to Biologic DMARDs (bDMARDs)

Summary

EudraCT number	2015-003335-35
Trial protocol	DE BE IE ES DK CZ SE GB HU NO SK PT LV AT FI GR FR BG SI
Global end of trial date	28 February 2022

Results information

Result version number	v1 (current)
This version publication date	28 January 2023
First version publication date	28 January 2023

Trial information

Trial identification

Sponsor protocol code	M13-542
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02706847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objective of Period 1 (Day 1 to Week 24) was to compare the safety and efficacy of 30 mg once daily (QD) and 15 mg QD upadacitinib versus placebo for the treatment of signs and symptoms of participants with moderately to severely active rheumatoid arthritis (RA) who were on a stable dose of csDMARDs and had an inadequate response to or intolerance to at least 1 bDMARD.

The study objective of Period 2 (Week 24 to Week 260) was to evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in participants with RA who completed Period 1.

Protection of trial subjects:

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

Background therapy:

Subjects were to have been on csDMARD therapy ≥ 3 months and on a stable dose of csDMARD therapy (restricted to methotexate, chloroquine, hydroxychloroquine, sulfasalazine, or leflunomide) for ≥ 4 weeks prior to the first dose of study drug and were to remain on a stable dose until Week 24; the csDMARD dose was to be decreased only for safety reasons.

Evidence for comparator: -

Actual start date of recruitment	15 March 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	Ireland: 4
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 320

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Puerto Rico: 7
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 21
Worldwide total number of subjects	499
EEA total number of subjects	144

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)	363
From 65 to 84 years	135
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 152 sites in 26 countries. Between March 2016, and January 2017, 778 patients were screened, of which 279 patients were excluded. A total of 499 patients were randomised; one patient withdrew from the upadacitinib 15 mg group before the start of study treatment because of accidental randomisation.

Pre-assignment

Screening details:

Participants were randomised (1:1:2:2) to either receive placebo for 12 weeks followed by upadacitinib 15 mg or 30 mg from week 12 onwards, or to receive upadacitinib 15 mg or 30 mg. Randomisation was stratified by the number of previous bDMARDs used and geographic region. For all analyses up to Week 12 the placebo groups were combined.

Period 1

Period 1 title	Period 1: Day 1 to Week 24
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Within the placebo group, 85 participants were assigned to receive placebo followed by upadacitinib 15 mg from Week 12 onwards and 84 participants were assigned to receive placebo followed by upadacitinib 30 mg from Week 12 onwards. Of these, 72 participants completed study drug through Week 12 and then received upadacitinib 15 mg and 75 participants completed study drug through Week 12 and then received upadacitinib 30 mg.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to receive placebo once daily for 12 weeks. At Week 12 participants were switched to either upadacitinib 15 mg or upadacitinib 30 mg according to the original randomisation scheme.

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

Dosage and administration details:

Matching placebo tablet

Arm title	Upadacitinib 15 mg
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Arm description:

Participants randomized to receive upadacitinib 15 mg once daily for 12 weeks followed by upadacitinib 15 mg once daily from Week 12 to Week 24.

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

Dosage and administration details:

Tablet for oral administration

Arm title	Upadacitinib 30 mg
Arm description:	
Participants randomized to receive upadacitinib 30 mg once daily for 12 weeks followed by upadacitinib 30 mg once daily from Week 12 to Week 24.	
Arm type	Experimental
Investigational medicinal product name	Upadacitinib
Investigational medicinal product code	ABT-494
Other name	RINVOQ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet for oral administration

Number of subjects in period 1^[1]	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
Started	169	164	165
Received Study Treatment	169	164	165
Completed Week 12 study participation	151	157	149
Completed Week 12 study drug	147	156	148
Completed	146	153	135
Not completed	23	11	30
Consent withdrawn by subject	5	5	6
Adverse event, non-fatal	7	3	17
Other	4	2	4
Lost to follow-up	3	-	1
Lack of efficacy	4	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One participant was randomised in error and did not receive study drug. This subject is not included in the disposition tables.

Period 2

Period 2 title	Period 2: Week 24 to Week 260
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Starting with Amendment 4, all subjects received open-label upadacitinib 15 mg QD, including those currently on upadacitinib 30 mg QD. Study sites and subjects were no longer blinded after this point.

Arms

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

Arm description:

Participants originally randomized to placebo then upadacitinib 15 mg received upadacitinib 15 mg once daily from Week 24 to Week 260.

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

Dosage and administration details:

Tablet for oral administration

Arm title	Placebo / Upadacitinib 30 mg
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Arm description:

Participants originally randomized to placebo then upadacitinib 30 mg received upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg.

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

Dosage and administration details:

Tablet for oral administration

Arm title	Upadacitinib 15 mg
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Arm description:

Participants originally randomized to receive upadacitinib 15 mg continued to receive upadacitinib 15 mg once daily from Week 24 to Week 260.

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

Dosage and administration details:

Tablet for oral administration

Arm title	Upadacitinib 30 mg
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Arm description:

Participants originally randomized to receive upadacitinib 30 mg continued to receive upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg.

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

Number of subjects in period 2^[2]	Placebo / Upadacitinib 15 mg	Placebo / Upadacitinib 30 mg	Upadacitinib 15 mg
Started	71	73	152
Switched to Upadacitinib 15 mg	0 ^[3]	44	0 ^[4]
Completed	35	41	81
Not completed	36	32	71
Consent withdrawn by subject	11	10	17
Adverse event, non-fatal	11	9	21
Other	8	5	15
Lost to follow-up	1	5	9
Lack of efficacy	5	3	9

Number of subjects in period 2^[2]	Upadacitinib 30 mg
Started	132
Switched to Upadacitinib 15 mg	94
Completed	82
Not completed	50
Consent withdrawn by subject	10
Adverse event, non-fatal	11
Other	15
Lost to follow-up	6
Lack of efficacy	8

Notes:

[2] - 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: Six participants completed the Week 24 visit but did not continue into Period 2.

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

Justification: Not applicable - participants in this group did not switch doses.

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

Justification: Not applicable - participants in this group did not switch doses.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Participants randomised to receive placebo once daily for 12 weeks. At Week 12 participants were switched to either upadacitinib 15 mg or upadacitinib 30 mg according to the original randomisation scheme.	
Reporting group title	Upadacitinib 15 mg
Reporting group description: Participants randomized to receive upadacitinib 15 mg once daily for 12 weeks followed by upadacitinib 15 mg once daily from Week 12 to Week 24.	
Reporting group title	Upadacitinib 30 mg
Reporting group description: Participants randomized to receive upadacitinib 30 mg once daily for 12 weeks followed by upadacitinib 30 mg once daily from Week 12 to Week 24.	

Reporting group values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
Number of subjects	169	164	165
Age categorical			
Units: Subjects			
< 40 years	14	11	14
40 - 64 years	106	115	103
≥ 65 years	49	38	48
Age continuous			
Units: years			
arithmetic mean	57.6	56.3	57.3
standard deviation	± 11.39	± 11.34	± 11.55
Gender categorical			
Units: Subjects			
Female	143	137	138
Male	26	27	27
Ethnicity			
Units: Subjects			
Hispanic or Latino	24	34	28
Not Hispanic or Latino	145	130	137
Race			
Units: Subjects			
White	143	142	148
Black or African American	21	17	10
American Indian/Alaska Native	0	3	4
Native Hawaiian or other Pacific Islander	0	0	1
Asian	5	2	2
Geographic Region			
Other includes Australia, New Zealand, and Israel.			
Units: Subjects			
North America	110	109	109
Western Europe	33	32	32
Eastern Europe	23	22	22

Asia	0	0	1
Other	3	1	1
Prior Failed Biological Disease-modifying Anti-rheumatic Drugs (bDMARDs)			
Randomization was stratified by the number of previous bDMARDs used: Stratum 1 consisted of participants who had inadequate response or intolerance to one or two biologics of the same class; Stratum 2 consisted of participants who had inadequate response or intolerance to at least three biologics of the same class and/or at least two biologics with different mechanisms of action.			
Units: Subjects			
Stratum 1	117	116	111
Stratum 2	52	48	54
Concomitant Conventional Synthetic DMARD Use at Baseline			
Units: Subjects			
Methotrexate alone	122	118	124
Methotrexate and other csDMARD	17	19	11
csDMARD other than methotrexate	29	24	29
Missing	1	3	1
Duration of RA Diagnosis			
Units: years			
arithmetic mean	14.5	12.4	12.7
standard deviation	± 9.22	± 9.38	± 9.65
Tender Joint Count			
A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: joints			
arithmetic mean	28.5	27.8	27.3
standard deviation	± 15.27	± 16.31	± 15.23
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: joints			
arithmetic mean	16.3	17.0	17.2
standard deviation	± 9.58	± 10.75	± 11.37
Patient's Assessment of Pain			
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." There were 166 participants, 163 participants, and 161 participants with available data in each treatment group, respectively.			
Units: mm			
arithmetic mean	68.9	68.2	65.3
standard deviation	± 21.03	± 19.77	± 20.67
Patient's Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 166 participants, 163 participants, and 163 participants with available data in each treatment group, respectively.			
Units: mm			
arithmetic mean	66.3	67.2	64.7
standard deviation	± 22.72	± 19.60	± 21.05
Physician's Global Assessment of Disease Activity			
The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 161 participants, 157 participants, and 157 participants with available data in each			

treatment group, respectively.			
Units: mm			
arithmetic mean	66.9	68.7	66.4
standard deviation	± 16.92	± 16.59	± 15.63
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
The HAQ-DI is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 (no disability) to 3 (very severe, high-dependency disability). There were 166, 163, and 161 participants with available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	1.6	1.7	1.6
standard deviation	± 0.60	± 0.64	± 0.59
High-sensitivity C-reactive Protein (hsCRP)			
Units: mg/L			
arithmetic mean	16.3	16.2	16.0
standard deviation	± 21.10	± 18.62	± 21.23
Disease Activity Score 28 Based on CRP (DAS28[CRP])			
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. There were 166, 163, and 163 participants with available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	5.8	5.9	5.8
standard deviation	± 1.00	± 0.95	± 0.89

Reporting group values	Total		
Number of subjects	498		
Age categorical			
Units: Subjects			
< 40 years	39		
40 - 64 years	324		
≥ 65 years	135		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	418		
Male	80		
Ethnicity			
Units: Subjects			
Hispanic or Latino	86		
Not Hispanic or Latino	412		
Race			
Units: Subjects			
White	433		
Black or African American	48		
American Indian/Alaska Native	7		

Native Hawaiian or other Pacific Islander	1		
Asian	9		
Geographic Region			
Other includes Australia, New Zealand, and Israel.			
Units: Subjects			
North America	328		
Western Europe	97		
Eastern Europe	67		
Asia	1		
Other	5		
Prior Failed Biological Disease-modifying Anti-rheumatic Drugs (bDMARDs)			
Randomization was stratified by the number of previous bDMARDs used: Stratum 1 consisted of participants who had inadequate response or intolerance to one or two biologics of the same class; Stratum 2 consisted of participants who had inadequate response or intolerance to at least three biologics of the same class and/or at least two biologics with different mechanisms of action.			
Units: Subjects			
Stratum 1	344		
Stratum 2	154		
Concomitant Conventional Synthetic DMARD Use at Baseline			
Units: Subjects			
Methotrexate alone	364		
Methotrexate and other csDMARD	47		
csDMARD other than methotrexate	82		
Missing	5		
Duration of RA Diagnosis			
Units: years			
arithmetic mean			
standard deviation	-		
Tender Joint Count			
A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: joints			
arithmetic mean			
standard deviation	-		
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: joints			
arithmetic mean			
standard deviation	-		
Patient's Assessment of Pain			
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." There were 166 participants, 163 participants, and 161 participants with available data in each treatment group, respectively.			
Units: mm			
arithmetic mean			
standard deviation	-		
Patient's Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 166 participants, 163 participants, and 163 participants with available data in each			

treatment group, respectively.			
Units: mm arithmetic mean standard deviation	-		
Physician's Global Assessment of Disease Activity			
The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 161 participants, 157 participants, and 157 participants with available data in each treatment group, respectively.			
Units: mm arithmetic mean standard deviation	-		
Health Assessment Questionnaire - Disability Index (HAQ-DI)			
The HAQ-DI is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 (no disability) to 3 (very severe, high-dependency disability). There were 166, 163, and 161 participants with available data in each treatment group, respectively.			
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])			
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. There were 166, 163, and 163 participants with available data in each treatment group, respectively.			
Units: units on a scale arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants randomised to receive placebo once daily for 12 weeks. At Week 12 participants were switched to either upadacitinib 15 mg or upadacitinib 30 mg according to the original randomisation scheme.	
Reporting group title	Upadacitinib 15 mg
Reporting group description: Participants randomized to receive upadacitinib 15 mg once daily for 12 weeks followed by upadacitinib 15 mg once daily from Week 12 to Week 24.	
Reporting group title	Upadacitinib 30 mg
Reporting group description: Participants randomized to receive upadacitinib 30 mg once daily for 12 weeks followed by upadacitinib 30 mg once daily from Week 12 to Week 24.	
Reporting group title	Placebo / Upadacitinib 15 mg
Reporting group description: Participants originally randomized to placebo then upadacitinib 15 mg received upadacitinib 15 mg once daily from Week 24 to Week 260.	
Reporting group title	Placebo / Upadacitinib 30 mg
Reporting group description: Participants originally randomized to placebo then upadacitinib 30 mg received upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg.	
Reporting group title	Upadacitinib 15 mg
Reporting group description: Participants originally randomized to receive upadacitinib 15 mg continued to receive upadacitinib 15 mg once daily from Week 24 to Week 260.	
Reporting group title	Upadacitinib 30 mg
Reporting group description: Participants originally randomized to receive upadacitinib 30 mg continued to receive upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg.	

Primary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 12
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 12. 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. The full analysis set (FAS) included all randomized participants who received at least 1 dose of study drug. Participants who prematurely discontinued from study drug prior to Week 12 or for whom DAS28 data were missing at Week 12 were considered non-responders.	
End point type	Primary
End point timeframe: Week 12	

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169 ^[1]	164 ^[2]	165 ^[3]	
Units: percentage of participants				
number (confidence interval 95%)	14.2 (8.9 to 19.5)	43.3 (35.7 to 50.9)	42.4 (34.9 to 50.0)	

Notes:

[1] - Full analysis set

[2] - Full analysis set

[3] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of LDA Based on DAS28(CRP)
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.001 ^[5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	29.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.9
upper limit	38.3

Notes:

[4] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[5] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Statistical analysis title	Analysis of LDA Based on DAS28(CRP)
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.001 ^[7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	28.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	19
upper limit	37.4

Notes:

[6] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[7] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Primary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 12

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 12
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End point description:

The primary endpoint for United States (US)/Food and Drug Administration (FDA) regulatory purposes was ACR 20% response (ACR20) at Week 12. Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR20 response criteria:

1. $\geq 20\%$ improvement in 68-tender joint count;
2. $\geq 20\%$ improvement in 66-swollen joint count; and
3. $\geq 20\%$ improvement in at least 3 of the 5 following parameters:
 - i) Physician global assessment of disease activity;
 - ii) Patient global assessment of disease activity;
 - iii) Patient assessment of pain;
 - iv) Health Assessment Questionnaire - Disability Index (HAQ-DI);
 - v) High-sensitivity C-reactive protein (hsCRP).

Participants who prematurely discontinued from study drug prior to Week 12 or for whom ACR data were missing at Week 12 were considered non-responders.

End point type	Primary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169 ^[8]	164 ^[9]	165 ^[10]	
Units: percentage of participants				
number (confidence interval 95%)	28.4 (21.6 to 35.2)	64.6 (57.3 to 72.0)	56.4 (48.8 to 63.9)	

Notes:

[8] - Full analysis set

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR20 Response
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	< 0.001 ^[12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	36.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	26.2
upper limit	46.2

Notes:

[11] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[12] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Statistical analysis title	Analysis of ACR20 Response
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	< 0.001 ^[14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	28
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.8
upper limit	38.1

Notes:

[13] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[14] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Secondary: Change From Baseline in in Disease Activity Score 28 (CRP) at Week 12

End point title	Change From Baseline in in Disease Activity Score 28 (CRP) at Week 12
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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. Multiple imputation was used for missing data in this analysis.

End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165 ^[15]	163 ^[16]	161 ^[17]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.02 (-1.23 to -0.80)	-2.31 (-2.52 to -2.10)	-2.29 (-2.50 to -2.09)	

Notes:

[15] - Full analysis set participants with available data at Baseline

[16] - Full analysis set participants with available data at Baseline

[17] - Full analysis set participants with available data at Baseline

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in DAS28 (CRP)
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	< 0.001 ^[19]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-1.01

Notes:

[18] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[19] - Analysis of covariance (ANCOVA) model with treatment, prior biological DMARD use (stratum 1 vs stratum 2) and baseline value as covariates.

Statistical analysis title	Analysis of Change from Baseline in DAS28 (CRP)
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	< 0.001 ^[21]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	-0.99

Notes:

[20] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[21] - Analysis of covariance (ANCOVA) model with treatment, prior biological DMARD use (stratum 1 vs

stratum 2) and baseline value as covariates.

Secondary: Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

End point title	Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12
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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. Multiple imputation was used for missing data in this analysis.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165 ^[22]	163 ^[23]	160 ^[24]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.17 (-0.26 to -0.08)	-0.39 (-0.48 to -0.30)	-0.42 (-0.51 to -0.33)	

Notes:

[22] - Full analysis set participants with available data at Baseline

[23] - Full analysis set participants with available data at Baseline

[24] - Full analysis set participants with available data at Baseline

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in HAQ-DI
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	< 0.001 ^[26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	-0.1

Notes:

[25] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[26] - ANCOVA model with treatment, prior biological DMARD use (stratum 1 vs stratum 2) and baseline value as covariates.

Statistical analysis title	Analysis of Change from Baseline in HAQ-DI
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	< 0.001 ^[28]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.13

Notes:

[27] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[28] - ANCOVA model with treatment, prior biological DMARD use (stratum 1 vs stratum 2) and baseline value as covariates.

Secondary: Change From Baseline in Short-Form 36 (SF-36) Physical Component Score (PCS) at Week 12

End point title	Change From Baseline in Short-Form 36 (SF-36) Physical Component Score (PCS) at Week 12
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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.

A mixed effect model repeat measurement (MMRM) with data from observed cases to Week 12 was used in this analysis.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145 ^[29]	156 ^[30]	147 ^[31]	
Units: units on a scale				
least squares mean (confidence interval 95%)	2.39 (1.14 to 3.64)	5.83 (4.60 to 7.05)	7.02 (5.78 to 8.25)	

Notes:

[29] - Full analysis set participants with available data

[30] - Full analysis set participants with available data

[31] - Full analysis set participants with available data

Statistical analyses

Statistical analysis title	Analysis of Change from Baseline in SF-36 PCS
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	< 0.001 ^[33]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	3.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	5.15

Notes:

[32] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[33] - MMRM model with fixed effects of treatment, visit, and treatment-by-visit interaction, previous bDMARD use, and baseline value as covariate.

Statistical analysis title	Analysis of Change from Baseline in SF-36 PCS
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	< 0.001 ^[35]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	6.36

Notes:

[34] - The overall type I error rate of the primary and ranked key secondary endpoints for the two doses was controlled using a graphical multiple testing procedure. The adjusted p-value under multiplicity control is reported, with significance achieved if the adjusted p-value is less than 0.05.

[35] - MMRM model with fixed effects of treatment, visit, and treatment-by-visit interaction, previous bDMARD use, and baseline value as covariate.

Secondary: Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 12

End point title	Percentage of Participants With an American College of Rheumatology 50% (ACR50) Response at Week 12
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End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR50 response criteria:

1. $\geq 50\%$ improvement in 68-tender joint count;
2. $\geq 50\%$ improvement in 66-swollen joint count; and
3. $\geq 50\%$ improvement in at least 3 of the 5 following parameters:
 - i) Physician global assessment of disease activity;
 - ii) Patient global assessment of disease activity;
 - iii) Patient assessment of pain;
 - iv) Health Assessment Questionnaire - Disability Index (HAQ-DI);
 - v) High-sensitivity C-reactive protein (hsCRP).

Participants who prematurely discontinued from study drug prior to Week 12 or for whom ACR data were missing at Week 12 were considered non-responders.

End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169 ^[36]	164 ^[37]	165 ^[38]	
Units: percentage of participants				
number (confidence interval 95%)	11.8 (7.0 to 16.7)	34.1 (26.9 to 41.4)	35.8 (28.4 to 43.1)	

Notes:

[36] - Full analysis set

[37] - Full analysis set

[38] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR50 Response
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	< 0.001 ^[40]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	22.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.6
upper limit	31.1

Notes:

[39] - The nominal p-value is reported

[40] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Statistical analysis title	Analysis of ACR50 Response
Comparison groups	Placebo v Upadacitinib 30 mg

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	< 0.001 ^[42]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	23.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.1
upper limit	32.7

Notes:

[41] - The nominal p-value is reported

[42] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Secondary: Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 12

End point title	Percentage of Participants With an American College of Rheumatology 70% (ACR70) Response at Week 12
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End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR70 response criteria:

1. ≥ 70% improvement in 68-tender joint count;
2. ≥ 70% improvement in 66-swollen joint count; and
3. ≥ 70% improvement in at least 3 of the 5 following parameters:
 - i) Physician global assessment of disease activity;
 - ii) Patient global assessment of disease activity;
 - iii) Patient assessment of pain;
 - iv) Health Assessment Questionnaire - Disability Index (HAQ-DI);
 - v) High-sensitivity C-reactive protein (hsCRP).

Participants who prematurely discontinued from study drug prior to Week 12 or for whom ACR data were missing at Week 12 were considered non-responders.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169 ^[43]	164 ^[44]	165 ^[45]	
Units: percentage of participants				
number (confidence interval 95%)	6.5 (2.8 to 10.2)	11.6 (6.7 to 16.5)	23.0 (16.6 to 29.5)	

Notes:

[43] - Full analysis set

[44] - Full analysis set

[45] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR70 Response
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority ^[46]
P-value	= 0.11 ^[47]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	11.2

Notes:

[46] - The nominal p-value is reported

[47] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Statistical analysis title	Analysis of ACR70 Response
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	< 0.001 ^[49]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.1
upper limit	23.9

Notes:

[48] - The nominal p-value is reported

[49] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Secondary: Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 1

End point title	Percentage of Participants With an American College of Rheumatology 20% (ACR20) Response at Week 1
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End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR20 response criteria:

1. $\geq 20\%$ improvement in 68-tender joint count;
2. $\geq 20\%$ improvement in 66-swollen joint count; and
3. $\geq 20\%$ improvement in at least 3 of the 5 following parameters:
 - i) Physician global assessment of disease activity;
 - ii) Patient global assessment of disease activity;
 - iii) Patient assessment of pain;
 - iv) Health Assessment Questionnaire - Disability Index (HAQ-DI);
 - v) High-sensitivity C-reactive protein (hsCRP).

Participants who prematurely discontinued from study drug prior to Week 1 or for whom ACR data were missing at Week 1 were considered non-responders.

End point type	Secondary
End point timeframe:	
Baseline and Week 1	

End point values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	169 ^[50]	164 ^[51]	165 ^[52]	
Units: percentage of participants				
number (confidence interval 95%)	10.7 (6.0 to 15.3)	27.4 (20.6 to 34.3)	24.8 (18.3 to 31.4)	

Notes:

[50] - Full analysis set

[51] - Full analysis set

[52] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR20 Response at Week 1
Comparison groups	Placebo v Upadacitinib 15 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority ^[53]
P-value	< 0.001 ^[54]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	16.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	25.1

Notes:

[53] - The nominal p-value is reported

[54] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Statistical analysis title	Analysis of ACR20 Response at Week 1
Comparison groups	Placebo v Upadacitinib 30 mg
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	< 0.001 ^[56]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	14.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.1
upper limit	22.3

Notes:

[55] - The nominal p-value is reported

[56] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological DMARD use (stratum 1 vs stratum 2).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported for Weeks 1 to 12 (all participants) and from Weeks 1 to 260 for participants who received upadacitinib.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Placebo: Weeks 1-12
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Reporting group description:

Participants received placebo once daily for 12 weeks.

Reporting group title	Upadacitinib 15 mg: Weeks 1-12
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Reporting group description:

Participants received upadacitinib 15 mg once daily for 12 weeks.

Reporting group title	Upadacitinib 30 mg: Weeks 1-12
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Reporting group description:

Participants received upadacitinib 30 mg once daily for 12 weeks.

Reporting group title	Upadacitinib 15 mg: Weeks 1-260
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Reporting group description:

Participants originally randomized to upadacitinib 15 mg received upadacitinib 15 mg for 260 weeks and participants originally randomized to placebo followed by upadacitinib 15 mg received upadacitinib 15 mg from Week 12 to Week 260.

Reporting group title	Upadacitinib 30 mg: Weeks 1-260/Switch
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Reporting group description:

Participants originally randomized to upadacitinib 30 mg received upadacitinib 30 mg up to implementation of Protocol Amendment 4 (December 2019) and participants originally randomized to placebo followed by upadacitinib 30 mg received upadacitinib 30 mg from Week 12 up to Week 260 or implementation of Protocol Amendment 4.

Reporting group title	Upadacitinib 15 mg After Switch
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Reporting group description:

Participants who were receiving upadacitinib 30 mg in Period 2 were switched to receive upadacitinib 15 mg once daily after implementation of Protocol Amendment 4 (December 2019) up to Week 260.

Serious adverse events	Placebo: Weeks 1-12	Upadacitinib 15 mg: Weeks 1-12	Upadacitinib 30 mg: Weeks 1-12
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 169 (0.00%)	9 / 164 (5.49%)	12 / 165 (7.27%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) ACUTE PROMYELOCYTIC LEUKAEMIA			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
COLON CANCER METASTATIC			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
FOLLICULAR THYROID CANCER			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HAEMANGIOMA			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 IN SITU			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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 METASTATIC			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PANCREATIC CARCINOMA STAGE IV			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	2 / 165 (1.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL CANCER METASTATIC			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HAEMATOMA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
MAY-THURNER SYNDROME			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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
DEATH			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
FATIGUE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
MALAISE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC DEATH			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
GENITAL HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE POLYP			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HYPOXIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
NASAL OBSTRUCTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PLEURAL EFFUSION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PNEUMONITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PULMONARY OEDEMA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 ARREST			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 FAILURE			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VOCAL CORD POLYP			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
ACUTE PSYCHOSIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ANXIETY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
DEPRESSION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 material issue			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 pacing issue			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
ANKLE FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
FALL			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
FOREARM FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FRACTURED SACRUM			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HEAD INJURY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HIP FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
INTENTIONAL OVERDOSE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PELVIC FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
POST PROCEDURAL FEVER			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN ABRASION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 COLUMN INJURY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ULNA FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
WOUND			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
ACUTE MYOCARDIAL INFARCTION			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ANGINA UNSTABLE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 TACHYCARDIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 FIBRILLATION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
Nervous system disorders			
ATAXIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
BELL'S PALSY			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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
DIZZINESS			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 RADICULOPATHY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
MYELOPATHY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SEIZURE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 CLAUDICATION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SPONDYLITIC MYELOPATHY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 ISCHAEMIC ATTACK			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS ISCHAEMIC			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ENTERITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC ULCER			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 PERFORATION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
NAUSEA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PERITONEAL HAEMATOMA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VOLVULUS OF SMALL BOWEL			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VOMITING			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
CHOLECYSTITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
CHOLESTASIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
GALLBLADDER POLYP			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
HIDRADENITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
DIABETIC FOOT			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
END STAGE RENAL DISEASE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 URINARY INCONTINENCE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
URETEROLITHIASIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
Endocrine disorders			
THYROID CYST			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
ANKLE DEFORMITY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ARTHRALGIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
BACK PAIN			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
EXOSTOSIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 DEFORMITY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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

FRACTURE DELAYED UNION				
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 DEGENERATION				
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	
MUSCULAR WEAKNESS				
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	
OSTEOARTHRITIS				
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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	
RHABDOMYOLYSIS				
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SYNOVIAL CYST			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
APPENDICITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ASPERGILLUS INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
CAVERNOUS SINUS THROMBOSIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
CHEST WALL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 SINUSITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
DIVERTICULITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ESCHERICHIA INFECTION			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
FOURNIER'S GANGRENE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 DERMAL CYST			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
OPHTHALMIC HERPES ZOSTER			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC INFLAMMATORY DISEASE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
PERINEPHRIC ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	2 / 165 (1.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA INFLUENZAL			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
POST PROCEDURAL INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 TRACT INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SINUSITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
SINUSITIS ASPERGILLUS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
VIRAL INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	0 / 165 (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
VULVAL ABSCESS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
WOUND INFECTION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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			
DEHYDRATION			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
ELECTROLYTE IMBALANCE			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HYPONATRAEMIA			

subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
HYPOVOLAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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
OBESITY			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (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	Upadacitinib 15 mg: Weeks 1-260	Upadacitinib 30 mg: Weeks 1-260/Switch	Upadacitinib 15 mg After Switch
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 236 (36.86%)	71 / 240 (29.58%)	21 / 138 (15.22%)
number of deaths (all causes)	9	5	2
number of deaths resulting from adverse events	1	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE PROMYELOCYTIC LEUKAEMIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER CANCER			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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

BREAST CANCER			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
COLON CANCER METASTATIC			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
FOLLICULAR THYROID CANCER			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMANGIOMA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
MALIGNANT MELANOMA IN SITU			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 METASTATIC			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
PANCREATIC CARCINOMA STAGE IV			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
PROSTATE CANCER			

subjects affected / exposed	0 / 236 (0.00%)	2 / 240 (0.83%)	0 / 138 (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
RECTAL CANCER METASTATIC			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
UTERINE LEIOMYOMA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
DEEP VEIN THROMBOSIS			
subjects affected / exposed	5 / 236 (2.12%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	1 / 5	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HAEMATOMA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
HYPERTENSION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
MAY-THURNER SYNDROME			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ORTHOSTATIC HYPOTENSION			

subjects affected / exposed	0 / 236 (0.00%)	3 / 240 (1.25%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
SUPERFICIAL VEIN THROMBOSIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
FATIGUE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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

MALAISE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PYREXIA			
subjects affected / exposed	2 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC DEATH			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
GENITAL HAEMORRHAGE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
UTERINE POLYP			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
VAGINAL HAEMORRHAGE			

subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	2 / 138 (1.45%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
ASTHMA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	3 / 236 (1.27%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (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
HYPOXIA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
NASAL OBSTRUCTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (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
PNEUMONITIS			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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	7 / 236 (2.97%)	3 / 240 (1.25%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 8	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
PULMONARY OEDEMA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 ARREST			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
VOCAL CORD POLYP			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ANXIETY			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SUICIDE ATTEMPT			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 material issue			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 pacing issue			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
FALL			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

FOREARM FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
FRACTURED SACRUM			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
HEAD INJURY			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	2 / 240 (0.83%)	0 / 138 (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
HUMERUS FRACTURE			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
INTENTIONAL OVERDOSE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
PELVIC FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL FEVER			

subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SKIN ABRASION			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COLUMN INJURY			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (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
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
TIBIA FRACTURE			

subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ULNA FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	4 / 236 (1.69%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
ATRIAL TACHYCARDIA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			

subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CARDIAC FAILURE			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
CARDIAC FIBRILLATION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
VENTRICULAR TACHYCARDIA			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ATAXIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
BELL'S PALSY			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 RADICULOPATHY			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
MYELOPATHY			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			

subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 CLAUDICATION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SPONDYLITIC MYELOPATHY			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SYNCOPE			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 236 (0.00%)	2 / 240 (0.83%)	0 / 138 (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

ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
COLITIS ISCHAEMIC			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
CONSTIPATION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
ENTERITIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
GASTRIC ULCER			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 HAEMORRHAGE			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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 OBSTRUCTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
NAUSEA			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
PANCREATITIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
PERITONEAL HAEMATOMA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (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
VOLVULUS OF SMALL BOWEL			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
VOMITING			

subjects affected / exposed	0 / 236 (0.00%)	3 / 240 (1.25%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
CHOLELITHIASIS			
subjects affected / exposed	2 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (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
CHOLESTASIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
GALLBLADDER POLYP			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
HIDRADENITIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
DIABETIC FOOT			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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	1 / 236 (0.42%)	2 / 240 (0.83%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

END STAGE RENAL DISEASE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
STRESS URINARY INCONTINENCE			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETEROLITHIASIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
Endocrine disorders			
THYROID CYST			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ANKLE DEFORMITY			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ARTHRALGIA			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
BACK PAIN			
subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (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

BURSITIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CERVICAL SPINAL STENOSIS			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EXOSTOSIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
FOOT DEFORMITY			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
FRACTURE DELAYED UNION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
INTERVERTEBRAL DISC DEGENERATION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (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
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	2 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (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
MUSCULAR WEAKNESS			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
OSTEOARTHRITIS			
subjects affected / exposed	5 / 236 (2.12%)	7 / 240 (2.92%)	2 / 138 (1.45%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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	1 / 236 (0.42%)	2 / 240 (0.83%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL STENOSIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPONDYLOLISTHESIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNOVIAL CYST			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
ASPERGILLUS INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
BRONCHITIS			
subjects affected / exposed	2 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (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
COVID-19			
subjects affected / exposed	4 / 236 (1.69%)	1 / 240 (0.42%)	2 / 138 (1.45%)
occurrences causally related to treatment / all	2 / 4	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	3 / 236 (1.27%)	0 / 240 (0.00%)	2 / 138 (1.45%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAVERNOUS SINUS THROMBOSIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
CELLULITIS			
subjects affected / exposed	2 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST WALL ABSCESS			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
CHRONIC SINUSITIS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
DIVERTICULITIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA BACTERAEemia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
FOURNIER'S GANGRENE			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 / 236 (0.00%)	2 / 240 (0.83%)	0 / 138 (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
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
HERPES ZOSTER			

subjects affected / exposed	0 / 236 (0.00%)	2 / 240 (0.83%)	0 / 138 (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
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
INFECTED DERMAL CYST			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
INFLUENZA			
subjects affected / exposed	2 / 236 (0.85%)	3 / 240 (1.25%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPHTHALMIC HERPES ZOSTER			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
PELVIC INFLAMMATORY DISEASE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
PERINEPHRIC ABSCESS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			

subjects affected / exposed	5 / 236 (2.12%)	9 / 240 (3.75%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	4 / 5	9 / 10	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA INFLUENZAL			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
POST PROCEDURAL INFECTION			
subjects affected / exposed	0 / 236 (0.00%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
PYELONEPHRITIS			
subjects affected / exposed	1 / 236 (0.42%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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 / 236 (0.85%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			

subjects affected / exposed	2 / 236 (0.85%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
SINUSITIS ASPERGILLUS			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	2 / 240 (0.83%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
VIRAL INFECTION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
VULVAL ABSCESS			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
WOUND INFECTION			

subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
ELECTROLYTE IMBALANCE			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (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
HYPOKALAEMIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
HYPOVOLAEMIA			
subjects affected / exposed	1 / 236 (0.42%)	0 / 240 (0.00%)	0 / 138 (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
OBESITY			
subjects affected / exposed	0 / 236 (0.00%)	1 / 240 (0.42%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo: Weeks 1-12	Upadacitinib 15 mg: Weeks 1-12	Upadacitinib 30 mg: Weeks 1-12
Total subjects affected by non-serious adverse events subjects affected / exposed	68 / 169 (40.24%)	68 / 164 (41.46%)	78 / 165 (47.27%)
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	4 / 169 (2.37%) 4	3 / 164 (1.83%) 3	3 / 165 (1.82%) 3
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) PYREXIA subjects affected / exposed occurrences (all)	3 / 169 (1.78%) 4 1 / 169 (0.59%) 1 0 / 169 (0.00%) 0	0 / 164 (0.00%) 0 0 / 164 (0.00%) 0 3 / 164 (1.83%) 4	7 / 165 (4.24%) 7 0 / 165 (0.00%) 0 2 / 165 (1.21%) 2
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	2 / 169 (1.18%) 2 1 / 169 (0.59%) 2	4 / 164 (2.44%) 4 2 / 164 (1.22%) 2	3 / 165 (1.82%) 3 2 / 165 (1.21%) 2
Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all)	0 / 169 (0.00%) 0 2 / 169 (1.18%) 2	0 / 164 (0.00%) 0 3 / 164 (1.83%) 3	4 / 165 (2.42%) 4 1 / 165 (0.61%) 1
Investigations BLOOD CREATINE PHOSPHOKINASE INCREASED subjects affected / exposed occurrences (all)	0 / 169 (0.00%) 0	2 / 164 (1.22%) 2	3 / 165 (1.82%) 3
Injury, poisoning and procedural complications			

FALL subjects affected / exposed occurrences (all)	2 / 169 (1.18%) 3	1 / 164 (0.61%) 2	4 / 165 (2.42%) 4
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	9 / 169 (5.33%) 9	7 / 164 (4.27%) 7	8 / 165 (4.85%) 8
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	0 / 169 (0.00%) 0	0 / 164 (0.00%) 0	1 / 165 (0.61%) 1
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) VOMITING subjects affected / exposed occurrences (all)	3 / 169 (1.78%) 3 0 / 169 (0.00%) 0 6 / 169 (3.55%) 6 4 / 169 (2.37%) 4 1 / 169 (0.59%) 1	0 / 164 (0.00%) 0 4 / 164 (2.44%) 4 4 / 164 (2.44%) 5 6 / 164 (3.66%) 6 4 / 164 (2.44%) 5	4 / 165 (2.42%) 4 3 / 165 (1.82%) 3 5 / 165 (3.03%) 7 7 / 165 (4.24%) 7 5 / 165 (3.03%) 5
Skin and subcutaneous tissue disorders RASH subjects affected / exposed occurrences (all)	2 / 169 (1.18%) 2	0 / 164 (0.00%) 0	0 / 165 (0.00%) 0
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN	5 / 169 (2.96%) 5	1 / 164 (0.61%) 1	2 / 165 (1.21%) 4

subjects affected / exposed	4 / 169 (2.37%)	2 / 164 (1.22%)	0 / 165 (0.00%)
occurrences (all)	4	2	0
MUSCLE SPASMS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	1 / 165 (0.61%)
occurrences (all)	0	0	1
OSTEOARTHRITIS			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences (all)	0	0	0
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	0 / 165 (0.00%)
occurrences (all)	1	1	0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	10 / 169 (5.92%)	4 / 164 (2.44%)	6 / 165 (3.64%)
occurrences (all)	10	5	6
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	4 / 169 (2.37%)	7 / 164 (4.27%)	4 / 165 (2.42%)
occurrences (all)	4	7	4
COVID-19			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	0 / 165 (0.00%)
occurrences (all)	0	0	0
GASTROENTERITIS			
subjects affected / exposed	1 / 169 (0.59%)	1 / 164 (0.61%)	0 / 165 (0.00%)
occurrences (all)	1	1	0
HERPES ZOSTER			
subjects affected / exposed	1 / 169 (0.59%)	2 / 164 (1.22%)	2 / 165 (1.21%)
occurrences (all)	1	2	2
NASOPHARYNGITIS			
subjects affected / exposed	11 / 169 (6.51%)	7 / 164 (4.27%)	9 / 165 (5.45%)
occurrences (all)	11	8	9
PHARYNGITIS			
subjects affected / exposed	1 / 169 (0.59%)	0 / 164 (0.00%)	2 / 165 (1.21%)
occurrences (all)	1	0	2
PNEUMONIA			
subjects affected / exposed	0 / 169 (0.00%)	1 / 164 (0.61%)	1 / 165 (0.61%)
occurrences (all)	0	1	1

SINUSITIS			
subjects affected / exposed	2 / 169 (1.18%)	4 / 164 (2.44%)	1 / 165 (0.61%)
occurrences (all)	2	4	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	13 / 169 (7.69%)	13 / 164 (7.93%)	11 / 165 (6.67%)
occurrences (all)	13	14	11
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 169 (5.92%)	16 / 164 (9.76%)	9 / 165 (5.45%)
occurrences (all)	11	19	10
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	0 / 169 (0.00%)	0 / 164 (0.00%)	2 / 165 (1.21%)
occurrences (all)	0	0	2
HYPERLIPIDAEMIA			
subjects affected / exposed	1 / 169 (0.59%)	3 / 164 (1.83%)	1 / 165 (0.61%)
occurrences (all)	1	3	1

Non-serious adverse events	Upadacitinib 15 mg: Weeks 1-260	Upadacitinib 30 mg: Weeks 1-260/Switch	Upadacitinib 15 mg After Switch
Total subjects affected by non-serious adverse events			
subjects affected / exposed	196 / 236 (83.05%)	203 / 240 (84.58%)	59 / 138 (42.75%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	29 / 236 (12.29%)	19 / 240 (7.92%)	3 / 138 (2.17%)
occurrences (all)	32	22	3
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	4 / 236 (1.69%)	16 / 240 (6.67%)	1 / 138 (0.72%)
occurrences (all)	5	16	1
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	11 / 236 (4.66%)	14 / 240 (5.83%)	0 / 138 (0.00%)
occurrences (all)	11	15	0
PYREXIA			
subjects affected / exposed	13 / 236 (5.51%)	7 / 240 (2.92%)	2 / 138 (1.45%)
occurrences (all)	16	9	2
Respiratory, thoracic and mediastinal disorders			

COUGH subjects affected / exposed occurrences (all)	28 / 236 (11.86%) 36	19 / 240 (7.92%) 20	3 / 138 (2.17%) 3
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	13 / 236 (5.51%) 13	8 / 240 (3.33%) 9	1 / 138 (0.72%) 1
Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all)	9 / 236 (3.81%) 9	13 / 240 (5.42%) 13	2 / 138 (1.45%) 2
INSOMNIA subjects affected / exposed occurrences (all)	8 / 236 (3.39%) 8	13 / 240 (5.42%) 14	2 / 138 (1.45%) 2
Investigations BLOOD CREATINE PHOSPHOKINASE INCREASED subjects affected / exposed occurrences (all)	18 / 236 (7.63%) 21	27 / 240 (11.25%) 33	4 / 138 (2.90%) 4
Injury, poisoning and procedural complications FALL subjects affected / exposed occurrences (all)	14 / 236 (5.93%) 17	18 / 240 (7.50%) 24	7 / 138 (5.07%) 7
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	17 / 236 (7.20%) 19	19 / 240 (7.92%) 23	1 / 138 (0.72%) 1
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	12 / 236 (5.08%) 12	11 / 240 (4.58%) 13	1 / 138 (0.72%) 1
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	5 / 236 (2.12%) 7	13 / 240 (5.42%) 14	0 / 138 (0.00%) 0
CONSTIPATION subjects affected / exposed occurrences (all)	15 / 236 (6.36%) 16	9 / 240 (3.75%) 9	2 / 138 (1.45%) 2
DIARRHOEA			

subjects affected / exposed occurrences (all)	12 / 236 (5.08%) 14	23 / 240 (9.58%) 25	1 / 138 (0.72%) 1
NAUSEA subjects affected / exposed occurrences (all)	14 / 236 (5.93%) 15	19 / 240 (7.92%) 23	1 / 138 (0.72%) 1
VOMITING subjects affected / exposed occurrences (all)	14 / 236 (5.93%) 17	11 / 240 (4.58%) 12	0 / 138 (0.00%) 0
Skin and subcutaneous tissue disorders RASH subjects affected / exposed occurrences (all)	13 / 236 (5.51%) 13	16 / 240 (6.67%) 20	1 / 138 (0.72%) 1
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	26 / 236 (11.02%) 34	28 / 240 (11.67%) 37	4 / 138 (2.90%) 5
BACK PAIN subjects affected / exposed occurrences (all)	16 / 236 (6.78%) 19	15 / 240 (6.25%) 17	8 / 138 (5.80%) 8
MUSCLE SPASMS subjects affected / exposed occurrences (all)	8 / 236 (3.39%) 9	13 / 240 (5.42%) 14	1 / 138 (0.72%) 1
OSTEOARTHRITIS subjects affected / exposed occurrences (all)	8 / 236 (3.39%) 9	14 / 240 (5.83%) 15	3 / 138 (2.17%) 3
PAIN IN EXTREMITY subjects affected / exposed occurrences (all)	13 / 236 (5.51%) 16	8 / 240 (3.33%) 8	0 / 138 (0.00%) 0
RHEUMATOID ARTHRITIS subjects affected / exposed occurrences (all)	34 / 236 (14.41%) 53	39 / 240 (16.25%) 51	13 / 138 (9.42%) 17
Infections and infestations BRONCHITIS subjects affected / exposed occurrences (all)	27 / 236 (11.44%) 32	37 / 240 (15.42%) 41	0 / 138 (0.00%) 0
COVID-19			

subjects affected / exposed	10 / 236 (4.24%)	2 / 240 (0.83%)	7 / 138 (5.07%)
occurrences (all)	10	2	7
GASTROENTERITIS			
subjects affected / exposed	12 / 236 (5.08%)	15 / 240 (6.25%)	0 / 138 (0.00%)
occurrences (all)	13	20	0
HERPES ZOSTER			
subjects affected / exposed	22 / 236 (9.32%)	32 / 240 (13.33%)	8 / 138 (5.80%)
occurrences (all)	25	38	9
NASOPHARYNGITIS			
subjects affected / exposed	34 / 236 (14.41%)	41 / 240 (17.08%)	3 / 138 (2.17%)
occurrences (all)	67	56	4
PHARYNGITIS			
subjects affected / exposed	5 / 236 (2.12%)	13 / 240 (5.42%)	0 / 138 (0.00%)
occurrences (all)	5	15	0
PNEUMONIA			
subjects affected / exposed	14 / 236 (5.93%)	11 / 240 (4.58%)	0 / 138 (0.00%)
occurrences (all)	14	11	0
SINUSITIS			
subjects affected / exposed	22 / 236 (9.32%)	19 / 240 (7.92%)	2 / 138 (1.45%)
occurrences (all)	34	24	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	74 / 236 (31.36%)	67 / 240 (27.92%)	1 / 138 (0.72%)
occurrences (all)	116	116	1
URINARY TRACT INFECTION			
subjects affected / exposed	43 / 236 (18.22%)	49 / 240 (20.42%)	11 / 138 (7.97%)
occurrences (all)	77	79	13
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	9 / 236 (3.81%)	13 / 240 (5.42%)	3 / 138 (2.17%)
occurrences (all)	9	13	3
HYPERLIPIDAEMIA			
subjects affected / exposed	15 / 236 (6.36%)	7 / 240 (2.92%)	1 / 138 (0.72%)
occurrences (all)	16	7	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2016	Amendment 1 included revisions to the inclusion criteria to clarify requirements of pregnancy testing and women of childbearing potential, to avoid ambiguity regarding RA classification criteria. Text was added to clarify contraception requirements for background RA medication and follicle stimulating hormone (FSH) testing for females, including adding countries with local requirements. Criteria were added for adjusting or adding background medication at Week 24 if subjects did not achieve LDA as defined by clinical disease activity index (CDAI). Text was added to clarify tuberculosis (TB) assessment and testing, electrocardiogram (ECG) procedures, and the CDAI calculation.
10 October 2016	Amendment 2 was updated to clarify that there were different primary efficacy variables for different regulatory purposes. Revisions updated inclusion criteria text to accommodate geographic differences in methotrexate dosing, to remove failure of csDMARDs, and to be more in line with expected pharmacodynamics of these drugs and standard practice. Revisions were made to the exclusion criteria to clarify the highest risk for gastrointestinal (GI) perforation with interleukin (IL)-6 and Janus kinase (JAK) inhibitors is for the lower GI tract, to update laboratory values within the screening period to reflect normal laboratory value reference ranges in the elderly population, and to reflect lack of QTc prolongation with upadacitinib. Guidance text was provided for washout of csDMARDs and permitted background RA therapy. Traditional Chinese medicine was added as prohibited. ECG and in vivo biomarkers at the final/premature discontinuation visit were added to the schedule of activities.
26 October 2017	Amendment 3 changed ABT-494 to upadacitinib throughout the protocol. Prohibited Therapy Examples of Commonly Used Strong cytochrome (CYP)3A Inhibitors and Inducers was updated, and clarified that live vaccines are prohibited during study participation. Contraception recommendations were updated, including the required duration of contraception recommendations for males, and clarification of allowed contraception for women. Study procedures regarding TB prophylaxis were revised. Updates were made to the ranked key secondary endpoints, other key secondary endpoints and additional endpoints to be aligned with the statistical analysis plan. Updates were made to the adverse events of special interest and the definition for assessing the relationship of adverse events to use of study drug per sponsor guidelines. Text was added to implement supplemental electronic case report form (eCRF) for thrombotic events. Updates were made to clarify the collection period for pregnancies occurring during study and the periods for avoiding pregnancy and sperm donation. Toxicity management was updated regarding clinically significant ECGs and abnormal laboratory values, international normalized ratio (INR) testing requirements, serum creatinine levels, and procedures for elevated creatine phosphokinase (CPK) value. Wording was added for management of subjects with Hepatitis B core antibody (HBc Ab)+ and negative hepatitis B virus DNA at screening and laboratory values during study which may indicate active hepatitis. Last observation carried forward (LOCF) analysis of the primary endpoint was removed to align with the statistical analysis plan. Clarifications were added that severity grading of abnormal labs will be based on Outcome Measures in Rheumatology (OMERACT) criteria (Rheumatology Common Toxicity Criteria v.2.0) or National Cancer Institute Common Terminology Criteria (NCI CTC).

13 December 2019	Amendment 4 included a change in the length of study from 240 weeks to 260 weeks to collect long-term safety data up to 5 years, and a change of dosing for all subjects to 15 mg QD open-label. Text was added to explain that unblinded hsCRP results would be sent to sites. Text was added to clarify that restarting study drug after an interruption of > 30 consecutive days is at the discretion of the Investigator. Prohibited Therapy section was updated to clarify that concurrent use of JAK inhibitors is prohibited during the study, to exclude biologic therapies, to allow high potency opiates for analgesic care related to AEs or SAEs, and to provide guidance for the use of live vaccine administration during Period 2. Contraception requirements for males were removed. Study procedures were updated to add guidance for interpretation of positive TB testing results in low risk subjects and the ability to retest locally to confirm central laboratory results, to add use of Interferon Gamma Release Assay as a substitute for local TB testing, and to specify that only subjects with newly identified TB risks are subject to chest x-rays. An additional discontinuation criteria was added regarding thrombosis events. Blinding of data for the Data Monitoring Committee (DMC) was revised to specify that the DMC concluded its oversight of the study after the end of Period 1. The study drug accountability requirements were updated according to the revised sponsor guidelines. Text was added in Adverse Events of Special Interest to clarify that all cardiac, embolic, and thrombotic events will be adjudicated. In Toxicity Management herpes zoster and a recommendation for skin examination were added, and the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) parameters for management were updated. In vivo pharmacodynamic biomarkers will not be collected at the Final visit.
30 June 2020	Amendment 5 included an update to clarify guidance for the use of live vaccine administration during Period 2 such that if a live vaccine must be administered during study participation, study drug must be held for at least 30 days prior to the vaccination and at least 30 days after the vaccination (or longer if required locally). The removal of male contraception requirements for upadacitinib were clarified, as based on the calculated safety margins for human fetal exposure with seminal fluid transfer, risks to a fetus from a male taking the study drug are not anticipated. Language was added regarding male contraception to indicate that male subjects receiving background csDMARDs during the study should follow contraception requirements for csDMARDs in accordance with the prescribing information for the background csDMARD.
08 December 2020	Amendment 6 included changes in response to the Coronavirus Disease – 19 (COVID-19) pandemic (or any state of emergency). An evaluation of the benefit and risk to subjects participating in the study relative to COVID-19 was added. Provisions for virtual or alternative locations for study visits due to the pandemic or any state of emergency were added. Clarifications were added regarding study activities that can be performed by phone/video conference or at local clinic/hospital/laboratory or through the optional home healthcare service in the event study visits are impacted by any state of emergency or pandemic situation. Study Procedures, including questionnaires, TB testing, chest X-rays, ECG, physical exam, efficacy assessments, laboratory tests, and pregnancy tests were updated to include provisions if an onsite visit cannot be performed due to the pandemic. Discontinuation criteria were revised regarding GI perforation and mitigation strategies related to the pandemic. Provision of study drug through direct-to-patient shipment was added. Language was added to include provision for modifications due to protocol deviations that may be due to the pandemic. Provisions allowing verbal consent in addition to the study informed consent were added. Supplemental COVID-19 case report forms were added. Text was added to define pregnancy and product complaint reporting timeline as 24 hours from site staff awareness. Guidance was added for investigators on the management of subjects with suspected or confirmed COVID-19 infection. A clarification was added that the Investigator should also contact the AbbVie TA MD for confirmed ALT or AST > 8 x ULN in addition to immediate study drug interruption. The list of examples of commonly used strong cytochrome 3A inducers and the list of the adverse events of special interest was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29908670>