Clinical trial results:
A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs

Summary

EudraCT number	2015-003332-13
Trial protocol	SK ES BG CZ DK BE IE PT GB PL LV FI NO LT HU GR AT RO HR IT
Global end of trial date	10 March 2022

Results information

Result version number	v1 (current)
This version publication date	08 March 2023
First version publication date	08 March 2023

Trial information

Trial identification

Sponsor protocol code	M13-549

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02675426
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	10 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to compare the efficacy, safety, and tolerability of upadacitinib 30 mg once daily (QD) and 15 mg QD versus placebo for the treatment of signs and symptoms of adults with moderately to severely active rheumatoid arthritis who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2015
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	Czechia: 24
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Kazakhstan: 1
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Slovakia: 13

Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 255
Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bosnia and Herzegovina: 10
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Croatia: 19
Worldwide total number of subjects	661
EEA total number of subjects	220

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)	509
From 65 to 84 years	151
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 149 centers in 35 countries in North America, eastern and western Europe, Asia, South America, Australia, New Zealand, and South Africa.
The study included a 12-week placebo-controlled, double-blind period (Period 1), and a 5-year (248 week) double-blind extension (Period 2).

Pre-assignment

Screening details:

Participants were randomly assigned in a 1:1:2:2 ratio to receive either 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. Randomization was stratified by prior exposure to biologic disease-modifying anti-rheumatic drug (bDMARD) and geographical region.

Period 1

Period 1 title	Period 1: Week 1 to Week 12
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor, Data analyst

Blinding implementation details:

Within the placebo group, 110 participants were assigned to receive placebo followed by upadacitinib 15 mg from Week 12 onwards and 111 participants were assigned to receive placebo followed by upadacitinib 30 mg from Week 12 onwards.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo once daily for 12 weeks in Period 1.

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

Dosage and administration details:

Administered orally once a day.

Arm title	Upadacitinib 15 mg

Arm description:

Participants received upadacitinib 15 mg once daily for 12 weeks in Period 1.

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

Dosage and administration details:

Administered orally once a day.

Arm title	Upadacitinib 30 mg

Arm description:

Participants received upadacitinib 30 mg once daily for 12 weeks in Period 1.

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

Dosage and administration details:

Administered orally once a day.

Number of subjects in period 1	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
Started	221	221	219
Received Study Drug	221	221	219
Completed	208	213	201
Not completed	13	8	18
Consent withdrawn by subject	3	5	5
Adverse event, non-fatal	6	3	9
Other	3	-	2
Lost to follow-up	1	-	2

Period 2

Period 2 title	Period 2: Week 12 to Week 260
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Subjects who were assigned to upadacitinib in Period 1 continued to receive blinded upadacitinib per original randomization assignment. Subjects assigned to placebo in Period 1 received upadacitinib 15 mg QD or 30 mg QD from Week 12 onward in a blinded fashion per pre-specified randomization assignments.
Study sites and subjects remained blinded until implementation of Protocol Amendment 6.0, when all subjects received upadacitinib 15 mg QD, with the earliest switch occurring at Week 168 visit.

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 12 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:

Administered orally once a day.

Arm title	Placebo / Upadacitinib 30 mg

Arm description:

Participants originally randomized to placebo then upadacitinib 30 mg received upadacitinib 30 mg once daily from Week 12 to Week 260. After Protocol Amendment 6 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:

Administered orally once a day.

Arm title	Upadacitinib 15 mg / Upadacitinib 15 mg

Arm description:

Participants originally randomized to receive upadacitinib 15 mg continued to receive upadacitinib 15 mg once daily for an additional 248 weeks in Period 2.

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

Dosage and administration details:

Administered orally once a day.

Arm title	Upadacitinib 30 mg / Upadacitinib 30 mg

Arm description:

Participants originally randomized to receive upadacitinib 30 mg continued to receive upadacitinib 30 mg for an additional 248 weeks or until implementation of Protocol Amendment 6 at which time participants were switched to receive upadacitinib 15 mg once daily.

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:

Administered orally once a day.

Number of subjects in period 2[1]	Placebo / Upadacitinib 15 mg	Placebo / Upadacitinib 30 mg	Upadacitinib 15 mg / Upadacitinib 15 mg
Started	103	103	212
Received Study Drug	103	102	207
Switched to Upadacitinib 15 mg	0 [2]	53	0 [3]
Completed	61	49	130
Not completed	42	54	82
Consent withdrawn by subject	14	21	31
Coronavirus Disease – 2019 (COVID-19) Infection	1	-	-
Adverse event, non-fatal	13	16	17
Other	8	12	23
COVID-19 Logistic Restrictions	1	-	1
Lost to follow-up	5	5	10

Number of subjects in period 2[1]	Upadacitinib 30 mg / Upadacitinib 30 mg
Started	200
Received Study Drug	199
Switched to Upadacitinib 15 mg	126
Completed	120
Not completed	80
Consent withdrawn by subject	30
Coronavirus Disease – 2019 (COVID-19) Infection	1
Adverse event, non-fatal	30
Other	15
COVID-19 Logistic Restrictions	-
Lost to follow-up	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Four participants completed the Week 12 visit but did not continue into Period 2.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not applicable - participants in this group did not switch doses.

[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.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once daily for 12 weeks in Period 1.	
Reporting group title	Upadacitinib 15 mg
Reporting group description:	
Participants received upadacitinib 15 mg once daily for 12 weeks in Period 1.	
Reporting group title	Upadacitinib 30 mg
Reporting group description:	
Participants received upadacitinib 30 mg once daily for 12 weeks in Period 1.	

Reporting group values	Placebo	Upadacitinib 15 mg	Upadacitinib 30 mg
Number of subjects	221	221	219
Age categorical Units: Subjects			
< 40 years	21	23	22
40 to 64 years	145	153	145
≥ 65 years	55	45	52
Age continuous Units: years			
arithmetic mean	56.0	55.3	55.8
standard deviation	± 12.22	± 11.47	± 11.29
Gender categorical Units: Subjects			
Female	166	182	172
Male	55	39	47
Race Units: Subjects			
White	187	188	186
Black or African American	10	13	8
American Indian / Alaskan Native	1	0	1
Asian	19	19	21
Multiple	4	1	3
Ethnicity Units: Subjects			
Hispanic or Latino	27	23	30
Not Hispanic or Latino	194	198	189
Geographical Region			
Other includes Australia, New Zealand, and South Africa.			
Units: Subjects			
North America	90	88	89
South/Central America	8	10	11
Western Europe	24	22	23
Eastern Europe	74	76	73
Asia	16	17	15
Other	9	8	8
Prior Biological DMARD Use			

Units: Subjects			
Yes	29	27	28
No	192	194	191
Conventional Synthetic DMARD (csDMARD) Use at Baseline Units: Subjects			
Methotrexate alone	141	122	136
Methotrexate and other csDMARD	49	47	39
csDMARD other than methotrexate	30	51	44
Missing	1	1	0
Duration of Rheumatoid Arthritis (RA) Diagnosis Units: years			
arithmetic mean	7.2	7.3	7.3
standard deviation	± 7.45	± 7.89	± 7.86
Tender Joint Count			
A total of 68 joints were assessed for the presence or absence of tenderness.			
Units: tender joints			
arithmetic mean	24.7	25.2	26.2
standard deviation	± 14.96	± 13.80	± 14.26
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: swollen joints			
arithmetic mean	15.4	16.0	16.2
standard deviation	± 9.24	± 10.04	± 10.55
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. A score of 0 indicates "no pain" and a score of 100 indicates "worst possible pain." There were 221, 217, and 219 subjects with available data in each treatment group respectively.			
Units: units on a scale			
arithmetic mean	61.5	64.1	64.0
standard deviation	± 20.80	± 19.45	± 19.77
Patient’s Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours ranging from 0 to 100 using a VAS, where 0 indicates very low disease activity and 100 indicates very high disease activity. There were 221, 217, and 219 subjects with available data in each treatment group respectively.			
Units: units on a scale			
arithmetic mean	60.3	63.1	62.8
standard deviation	± 20.50	± 21.86	± 20.32
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, where 0 indicates very low disease activity and 100 indicates very high disease activity. There were 211, 209, and 213 subjects with available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	64.4	64.3	63.0
standard deviation	± 17.67	± 16.22	± 17.99
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 221, 216, and 219 subjects with available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	1.4	1.5	1.5
standard deviation	± 0.63	± 0.61	± 0.61
High-sensitivity C-reactive Protein (hsCRP)			
Units: mg/L			
arithmetic mean	12.6	16.6	14.8
standard deviation	± 13.96	± 19.17	± 16.86
Disease Activity Score 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 221, 217, and 219 participants with available data in each treatment group, respectively.			
Units: units on a scale			
arithmetic mean	5.6	5.7	5.7
standard deviation	± 0.84	± 0.97	± 0.90

Reporting group values	Total		
Number of subjects	661		
Age categorical			
Units: Subjects			
< 40 years	66		
40 to 64 years	443		
≥ 65 years	152		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	520		
Male	141		
Race			
Units: Subjects			
White	561		
Black or African American	31		
American Indian / Alaskan Native	2		
Asian	59		
Multiple	8		
Ethnicity			
Units: Subjects			
Hispanic or Latino	80		
Not Hispanic or Latino	581		
Geographical Region			
Other includes Australia, New Zealand, and South Africa.			
Units: Subjects			
North America	267		
South/Central America	29		

Western Europe	69		
Eastern Europe	223		
Asia	48		
Other	25		
Prior Biological DMARD Use Units: Subjects			
Yes	84		
No	577		
Conventional Synthetic DMARD (csDMARD) Use at Baseline Units: Subjects			
Methotrexate alone	399		
Methotrexate and other csDMARD	135		
csDMARD other than methotrexate	125		
Missing	2		
Duration of Rheumatoid Arthritis (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: tender joints arithmetic mean standard deviation	 -		
Swollen Joint Count			
A total of 66 joints were assessed for the presence or absence of swelling.			
Units: swollen 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. A score of 0 indicates "no pain" and a score of 100 indicates "worst possible pain." There were 221, 217, and 219 subjects with available data in each treatment group respectively.			
Units: units on a scale arithmetic mean standard deviation	 -		
Patient’s Global Assessment of Disease Activity			
The participant was asked to rate their current RA disease activity over the past 24 hours ranging from 0 to 100 using a VAS, where 0 indicates very low disease activity and 100 indicates very high disease activity. There were 221, 217, and 219 subjects with available data in each treatment group respectively.			
Units: units on a scale 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, where 0 indicates very low disease activity and 100 indicates very high disease activity. There were 211, 209, and 213 subjects with available data in each treatment group, respectively.			
Units: units on a scale arithmetic mean			

standard deviation	-		
Health Assessment Questionnaire – Disability Index (HAQ-DI)			
The HAQ-DI is a patient-reported questionnaire that measures the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and errands and chores) over the past week. Participants assessed their ability to do each task on a scale from 0 (without any difficulty) to 3 (unable to do). Scores were averaged to provide an overall score ranging from 0 (no disability) to 3 (very severe, high-dependency disability). There were 221, 216, and 219 subjects 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 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 221, 217, and 219 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 received placebo once daily for 12 weeks in Period 1.	
Reporting group title	Upadacitinib 15 mg
Reporting group description:	
Participants received upadacitinib 15 mg once daily for 12 weeks in Period 1.	
Reporting group title	Upadacitinib 30 mg
Reporting group description:	
Participants received upadacitinib 30 mg once daily for 12 weeks in Period 1.	
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 12 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 12 to Week 260. After Protocol Amendment 6 participants still on study were switched to receive upadacitinib 15 mg.	
Reporting group title	Upadacitinib 15 mg / Upadacitinib 15 mg
Reporting group description:	
Participants originally randomized to receive upadacitinib 15 mg continued to receive upadacitinib 15 mg once daily for an additional 248 weeks in Period 2.	
Reporting group title	Upadacitinib 30 mg / Upadacitinib 30 mg
Reporting group description:	
Participants originally randomized to receive upadacitinib 30 mg continued to receive upadacitinib 30 mg for an additional 248 weeks or until implementation of Protocol Amendment 6 at which time participants were switched to receive upadacitinib 15 mg once daily.	

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), 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 one 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	221[1]	221[2]	219[3]	
Units: percentage of participants				
number (confidence interval 95%)	17.2 (12.2 to 22.2)	48.4 (41.8 to 55.0)	47.9 (41.3 to 54.6)	

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	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	31.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	23
upper limit	39.5

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 disease-modifying anti-rheumatoid drug use.

Statistical analysis title	Analysis of LDA Based on DAS28(CRP)
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	30.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.5
upper limit	39

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 disease-modifying anti-rheumatoid drug use.

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

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. ≥ 20% improvement in 68-tender joint count;
2. ≥ 20% improvement in 66-swollen joint count; and
3. ≥ 20% improvement in at least 3 of the 5 following parameters:
 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

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	221[8]	221[9]	219[10]	
Units: percentage of participant				
number (confidence interval 95%)	35.7 (29.4 to 42.1)	63.8 (57.5 to 70.1)	66.2 (59.9 to 72.5)	

Notes:

[8] - Full analysis set

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR20 Response at Week 12
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	28.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.1
upper limit	37

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 disease-modifying anti-rheumatoid drug use.

Statistical analysis title	Analysis of ACR20 Response at Week 12
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	30.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.6
upper limit	39.4

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 disease-modifying anti-rheumatoid drug use.

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

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), 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	220[15]	217[16]	219[17]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.02 (-1.22 to -0.82)	-2.20 (-2.40 to -2.00)	-2.34 (-2.54 to -2.14)	

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	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.001 [19]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	-0.94

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 bDMARD use and Baseline value as covariates.

Statistical analysis title	Analysis of Change from Baseline in DAS28 (CRP)
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.001 [21]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	-1.08

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] - ANCOVA model with treatment, prior bDMARD use 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

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

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	220[22]	216[23]	219[24]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.25 (-0.34 to -0.17)	-0.59 (-0.67 to -0.51)	-0.54 (-0.62 to -0.46)	

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	436
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.001 [26]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.24

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 bDMARD use and Baseline value as covariates.

Statistical analysis title	Analysis of Change from Baseline in HAQ-DI

Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	439
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001 [28]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	-0.18

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 bDMARD use and Baseline value as covariates.

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

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

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 summary 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

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	207[29]	209[30]	197[31]	
Units: units on a scale				
least squares mean (confidence interval 95%)	3.03 (1.88 to 4.18)	7.58 (6.43 to 8.74)	8.01 (6.84 to 9.18)	

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	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	416
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	4.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.13
upper limit	5.98

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	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	404
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	4.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.54
upper limit	6.42

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 Achieving Clinical Remission Based on DAS28 (CRP) at Week 12

End point title	Percentage of Participants Achieving Clinical Remission Based on DAS28 (CRP) at Week 12

End point description:

Clinical remission (CR) based on DAS28 (CRP) is defined as achieving a DAS28 (CRP) of less than 2.6. 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), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity.
Participants who prematurely discontinued from study drug prior to Week 12 or for whom DAS28 (CRP) data were missing at Week 12 were considered non-responders.

End point type	Secondary

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	221[36]	221[37]	219[38]	
Units: percentage of participants				
number (confidence interval 95%)	10.0 (6.0 to 13.9)	30.8 (24.7 to 36.9)	28.3 (22.3 to 34.3)	

Notes:
[36] - Full analysis set
[37] - Full analysis set
[38] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of Clinical Remission Based on DAS28(CRP)
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.001 [40]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.6
upper limit	28.1

Notes:
[39] - 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.
[40] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use.

Statistical analysis title	Analysis of Clinical Remission Based on DAS28(CRP)
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.001 [42]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	18.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.2
upper limit	25.5

Notes:

[41] - 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.

[42] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use.

Secondary: Percentage of Participants Achieving Low Disease Activity Based on CDAI at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity Based on CDAI at Week 12

End point description:

Low disease activity based on the clinical disease activity index (CDAI) is defined as a CDAI score ≤ 10. CDAI is a composite index for assessing disease activity based on the summation of the total tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), patient global assessment of disease activity measured on a VAS from 0 to 10 cm, and physician global assessment of disease activity measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 78 with higher scores indicating higher disease activity.
Participants who prematurely discontinued from study drug prior to Week 12 or for whom CDAI data were missing at Week 12 were considered non-responders.

End point type	Secondary

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	221[43]	221[44]	219[45]	
Units: percentage of participants				
number (confidence interval 95%)	19.0 (13.8 to 24.2)	40.3 (33.8 to 46.7)	42.0 (35.5 to 48.5)	

Notes:

[43] - Full analysis set

[44] - Full analysis set

[45] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of LDA Based on CDAI
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	< 0.001 [47]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	21.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	13
upper limit	29.5

Notes:

[46] - 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.
[47] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use.

Statistical analysis title	Analysis of LDA Based on CDAI
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	< 0.001 [49]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.7
upper limit	31.3

Notes:

[48] - 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.
[49] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use.

Secondary: Change From Baseline in Duration of Morning Stiffness at Week 12

End point title	Change From Baseline in Duration of Morning Stiffness at Week 12

End point description:

Participants were asked to indicate the time it took for them to get as limber as possible after awakening with morning stiffness over the past 7 days.
A mixed effect model repeat measurement (MMRM) analysis with data from observed cases to Week 12 was used in the 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	202[50]	207[51]	197[52]	
Units: minutes				
least squares mean (confidence interval 95%)	-34.27 (-54.63 to -13.91)	-85.28 (-105.61 to -64.95)	-85.13 (-105.65 to -64.62)	

Notes:

[50] - Full analysis set participants with available data

[51] - Full analysis set participants with available data

[52] - Full analysis set participants with available data

Statistical analyses

Statistical analysis title	Analysis of Change in Morning Stiffness
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	< 0.001 [54]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-51.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.14
upper limit	-23.87

Notes:

[53] - 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.

[54] - 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 in Morning Stiffness
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	< 0.001 [56]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	-50.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78.19
upper limit	-23.53

Notes:

[55] - 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.

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

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

End point title	Change From Baseline in in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) at Week 12

End point description:

The FACIT-Fatigue scale is a 13-item tool that measures an individual's level of fatigue during their usual daily activities over the past 7 days. Each of the fatigue and impact of fatigue items are measured on a five point Likert scale from 0 (not at all) to 4 (very much). The FACIT-Fatigue scale is the sum of the individual 13 scores and ranges from 0 to 52 where higher scores indicate better the quality of life. A positive change from Baseline indicates improvement.
A mixed effect model repeat measurement (MMRM) analysis with data from observed cases to Week 12 was used in the 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	207[57]	207[58]	197[59]	
Units: units on a scale				
least squares mean (confidence interval 95%)	2.96 (1.62 to 4.30)	7.91 (6.56 to 9.27)	7.74 (6.38 to 9.11)	

Notes:

[57] - Full analysis set participants with available data

[58] - Full analysis set participants with available data

[59] - Full analysis set participants with available data

Statistical analyses

Statistical analysis title	Analysis of Change in FACIT-Fatigue
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	< 0.001 [61]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	4.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.31
upper limit	6.6

Notes:

[60] - 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.
[61] - 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 in FACIT-Fatigue
Comparison groups	Upadacitinib 30 mg v Placebo

Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	< 0.001 [63]
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	LS Mean Difference
Point estimate	4.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.12
upper limit	6.44

Notes:

[62] - 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.

[63] - 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

End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR50 response criteria:
1. ≥ 50% improvement in 68-tender joint count;
2. ≥ 50% improvement in 66-swollen joint count; and
3. ≥ 50% improvement in at least 3 of the 5 following parameters:
 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	221[64]	221[65]	219[66]	
Units: percentage of participants				
number (confidence interval 95%)	14.9 (10.2 to 19.6)	38.0 (31.6 to 44.4)	43.4 (36.8 to 49.9)	

Notes:

[64] - Full analysis set

[65] - Full analysis set

[66] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR50 Response
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [67]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	23.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.1
upper limit	31

Notes:

[67] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

Statistical analysis title	Analysis of ACR50 Response
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [68]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	28.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.4
upper limit	36.5

Notes:

[68] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

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

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

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	221[69]	221[70]	219[71]	
Units: percentage of participants				
number (confidence interval 95%)	5.9 (2.8 to 9.0)	20.8 (15.5 to 26.2)	26.5 (20.6 to 32.3)	

Notes:

[69] - Full analysis set

[70] - Full analysis set

[71] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR70 Response
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [72]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.7
upper limit	21.1

Notes:

[72] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

Statistical analysis title	Analysis of ACR70 Response
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [73]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	20.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	14
upper limit	27.2

Notes:

[73] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

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

End point description:

Participants who met the following 3 conditions for improvement from baseline were classified as meeting the ACR20 response criteria:
1. ≥ 20% improvement in 68-tender joint count;
2. ≥ 20% improvement in 66-swollen joint count; and
3. ≥ 20% improvement in at least 3 of the 5 following parameters:
 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	221[74]	221[75]	219[76]	
Units: percentage of participants				
number (confidence interval 95%)	8.6 (4.9 to 12.3)	22.2 (16.7 to 27.6)	28.3 (22.3 to 34.3)	

Notes:

[74] - Full analysis set

[75] - Full analysis set

[76] - Full analysis set

Statistical analyses

Statistical analysis title	Analysis of ACR20 Response at Week 1
Comparison groups	Upadacitinib 15 mg v Placebo
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [77]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	20.2

Notes:

[77] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

Statistical analysis title	Analysis of ACR20 Response at Week 1
Comparison groups	Upadacitinib 30 mg v Placebo
Number of subjects included in analysis	440
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [78]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	26.7

Notes:

[78] - Cochran-Mantel-Haenszel test adjusted for the stratification factor of prior biological disease-modifying anti-rheumatoid drug use. The unadjusted p-value is reported.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1: From first dose of study drug up to Week 12 or up to 30 days after last dose for participants who discontinued study drug prior to Week 12.
Period 1+2: From first dose of upadacitinib up to 30 days after last dose (maximum of 264 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Period 1: Placebo

Reporting group description:

Participants received placebo once daily for 12 weeks in Period 1.

Reporting group title	Period 1: Upadacitinib 15 mg

Reporting group description:

Participants received upadacitinib 15 mg once daily for 12 weeks in Period 1.

Reporting group title	Period 1: Upadacitinib 30 mg

Reporting group description:

Participants received upadacitinib 30 mg once daily for 12 weeks in Period 1.

Reporting group title	Period 1+2: Upadacitinib 15 mg

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	Period 1+2: Upadacitinib 30 mg

Reporting group description:

Participants originally randomized to upadacitinib 30 mg received upadacitinib 30 mg up to Week 260 or implementation of Protocol Amendment 6 (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 6.

Reporting group title	Period 2: Upadacitinib 15 mg After Switch

Reporting group description:

Participants who were receiving upadacitinib 30 mg in Period 2 were switched to upadacitinib 15 mg once daily after implementation of Protocol Amendment 6 (December 2019) up to Week 260.

Serious adverse events	Period 1: Placebo	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 221 (2.26%)	10 / 221 (4.52%)	7 / 219 (3.20%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACROCHORDON			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 OF COLON			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL CANCER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-CELL SMALL LYMPHOCYTIC LYMPHOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLEAR CELL RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CUTANEOUS T-CELL LYMPHOMA			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 CANCER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC CANCER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC CANCER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHANGIOSIS CARCINOMATOSA			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO SPINE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-HODGKIN'S LYMPHOMA STAGE IV			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN GERM CELL TERATOMA BENIGN			
subjects affected / exposed	0 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAPILLARY THYROID CANCER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PITUITARY TUMOUR BENIGN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 STAGE II			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 CANCER STAGE I			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEMINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 SQUAMOUS CELL CARCINOMA RECURRENT			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF LUNG			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THERAPY CHANGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (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
OEDEMA PERIPHERAL			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTHETIC CARDIAC VALVE STENOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 STENT OCCLUSION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
GENITAL PROLAPSE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CYST			
subjects affected / exposed	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (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 PAIN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 PROLAPSE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIECTASIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMPHYSEMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (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
ORGANISING PNEUMONIA			
subjects affected / exposed	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (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

PLEURAL EFFUSION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY MASS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
BEHAVIOUR DISORDER			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HALLUCINATION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
DEVICE BREAKAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCUS TEST POSITIVE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TROPONIN INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT DECREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
ACETABULUM FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA POSTOPERATIVE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 INJURY			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMMINUTED FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONTUSION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBULA FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 DISPLACEMENT			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAND FRACTURE			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION POSTOPERATIVE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 INJURIES			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 DISCHARGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 FISTULA			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 HAEMORRHAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCEDURAL PAIN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL INJURY			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WRIST FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	2 / 221 (0.90%)	0 / 219 (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
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (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
BRADYCARDIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 CHRONIC			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOLFF-PARKINSON-WHITE SYNDROME			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL INFARCTION			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBOSACRAL RADICULOPATHY			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT GLOBAL AMNESIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 PARALYSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA MACROCYTIC			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 LOSS ANAEMIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHADENITIS			

subjects affected / exposed	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
CORNEAL DECOMPENSATION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL TEAR			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ULCERATIVE KERATITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL FISSURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENAL STENOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSBIOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOPERITONEUM			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETROPERITONEAL HAEMORRHAGE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATOMEGALY			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

ANGIOEDEMA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DERMAL CYST			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	0 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (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
STRESS URINARY INCONTINENCE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL STENOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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			
GOITRE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FASCIITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FISTULA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT INSTABILITY			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	1 / 221 (0.45%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ROTATOR CUFF SYNDROME			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 PAIN			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENOSYNOVITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VERTEBRAL FORAMINAL STENOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VERTEBRAL OSTEOPHYTE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS BACTERIAL			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE TUBERCULOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 VIRAL			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 STAPHYLOCOCCAL			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHORIORETINITIS			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC ABSCESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS STAPHYLOCOCCAL			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	0 / 221 (0.00%)	1 / 221 (0.45%)	0 / 219 (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
ERYSIPELAS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EXTRADURAL ABSCESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EXTRAPULMONARY TUBERCULOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GROIN ABSCESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS B REACTIVATION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 CUTANEOUS DISSEMINATED			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ABSCESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METAPNEUMOVIRUS INFECTION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE ABSCESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECROTISING FASCIITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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	1 / 221 (0.45%)	0 / 221 (0.00%)	0 / 219 (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 STREPTOCOCCAL			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGO-OOPHORITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SIALOADENITIS			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TONSILLITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBERCULOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICELLA			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VESTIBULAR NEURONITIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION STAPHYLOCOCCAL			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
YERSINIA INFECTION			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LACTIC ACIDOSIS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
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 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 1+2: Upadacitinib 15 mg	Period 1+2: Upadacitinib 30 mg	Period 2: Upadacitinib 15 mg After Switch
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 324 (28.09%)	102 / 321 (31.78%)	19 / 179 (10.61%)
number of deaths (all causes)	4	7	2
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACROCHORDON			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ADENOCARCINOMA OF COLON			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ANAL CANCER			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
B-CELL SMALL LYMPHOCYTIC LYMPHOMA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
BOWEN'S DISEASE			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLEAR CELL RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
CUTANEOUS T-CELL LYMPHOMA			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOMETRIAL CANCER			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
GASTRIC CANCER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
HEPATIC CANCER			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
INVASIVE BREAST CARCINOMA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
INVASIVE DUCTAL BREAST CARCINOMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHANGIOSIS CARCINOMATOSA			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
MALIGNANT MELANOMA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
METASTASES TO SPINE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
NON-HODGKIN'S LYMPHOMA STAGE IV			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
OVARIAN GERM CELL TERATOMA BENIGN			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PAPILLARY THYROID CANCER			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
PITUITARY TUMOUR BENIGN			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
PROSTATE CANCER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 STAGE II			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
RENAL CANCER STAGE I			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
SEMINOMA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
SKIN SQUAMOUS CELL CARCINOMA RECURRENT			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
SQUAMOUS CELL CARCINOMA OF LUNG			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 LEIOMYOMA			
subjects affected / exposed	2 / 324 (0.62%)	1 / 321 (0.31%)	0 / 179 (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
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
HYPOTENSION			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
THERAPY CHANGE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PROSTHETIC CARDIAC VALVE STENOSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PYREXIA			
subjects affected / exposed	1 / 324 (0.31%)	3 / 321 (0.93%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 STENT OCCLUSION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Reproductive system and breast disorders			
GENITAL PROLAPSE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
OVARIAN CYST			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	0 / 179 (0.00%)
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 PAIN			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 PROLAPSE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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	3 / 324 (0.93%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
BRONCHIECTASIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	2 / 324 (0.62%)	1 / 321 (0.31%)	0 / 179 (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
EMPHYSEMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
HYPOXIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
ORGANISING PNEUMONIA			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	0 / 179 (0.00%)
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 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
PNEUMONITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PULMONARY EMBOLISM			
subjects affected / exposed	3 / 324 (0.93%)	2 / 321 (0.62%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	2 / 3	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY MASS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PULMONARY OEDEMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Psychiatric disorders			
BEHAVIOUR DISORDER			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
DEPRESSION			

subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
HALLUCINATION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 BREAKAGE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE MATERIAL ISSUE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Investigations			
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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

LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
STAPHYLOCOCCUS TEST POSITIVE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
TROPONIN INCREASED			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
WEIGHT DECREASED			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
WEIGHT INCREASED			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Injury, poisoning and procedural complications			
ACETABULUM FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ANAEMIA POSTOPERATIVE			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	2 / 324 (0.62%)	1 / 321 (0.31%)	0 / 179 (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

BACK INJURY			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
COMMINUTED FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
CONTUSION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	3 / 324 (0.93%)	0 / 321 (0.00%)	0 / 179 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
FEMUR FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBULA FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
FRACTURE DISPLACEMENT			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
HAND FRACTURE			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
INCISIONAL HERNIA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
JOINT DISLOCATION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
JOINT DISLOCATION POSTOPERATIVE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
MULTIPLE INJURIES			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
PELVIC FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
POST PROCEDURAL DISCHARGE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
POST PROCEDURAL FISTULA			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PROCEDURAL PAIN			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
RADIUS FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
RIB FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 COMPRESSION FRACTURE			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
TIBIA FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
UPPER LIMB FRACTURE			
subjects affected / exposed	1 / 324 (0.31%)	2 / 321 (0.62%)	0 / 179 (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
URETHRAL INJURY			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
WOUND			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
WRIST FRACTURE			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 324 (0.31%)	5 / 321 (1.56%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	4 / 324 (1.23%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
CARDIAC ARREST			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
WOLFF-PARKINSON-WHITE SYNDROME			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
CEREBRAL INFARCTION			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
CEREBROSPINAL FLUID LEAKAGE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
HEADACHE			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
LUMBOSACRAL RADICULOPATHY			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PRESYNCOPE			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
TRANSIENT GLOBAL AMNESIA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 PARALYSIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
ANAEMIA MACROCYTIC			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
BLOOD LOSS ANAEMIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
LYMPHADENITIS			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
CORNEAL DECOMPENSATION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
RETINAL DETACHMENT			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	0 / 179 (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
RETINAL TEAR			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
ULCERATIVE KERATITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ANAL FISSURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
COLITIS ISCHAEMIC			

subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
DUODENAL STENOSIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
DYSBIOSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
PNEUMOPERITONEUM			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RETROPERITONEAL HAEMORRHAGE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
UMBILICAL HERNIA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT STONE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
CHOLECYSTITIS			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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	1 / 324 (0.31%)	4 / 321 (1.25%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC STEATOSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
HEPATITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
HEPATOMEGALY			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

ANGIOEDEMA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
DERMAL CYST			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 324 (0.31%)	2 / 321 (0.62%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROLITHIASIS			
subjects affected / exposed	2 / 324 (0.62%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STRESS URINARY INCONTINENCE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
URETHRAL STENOSIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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			
GOITRE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
BACK PAIN			
subjects affected / exposed	2 / 324 (0.62%)	1 / 321 (0.31%)	0 / 179 (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
FASCIITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
FISTULA			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
FOOT DEFORMITY			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC DEGENERATION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 PROTRUSION			
subjects affected / exposed	2 / 324 (0.62%)	1 / 321 (0.31%)	0 / 179 (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
JOINT INSTABILITY			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	3 / 324 (0.93%)	0 / 321 (0.00%)	0 / 179 (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
NECK PAIN			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
OSTEOARTHRITIS			
subjects affected / exposed	6 / 324 (1.85%)	8 / 321 (2.49%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 11	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
ROTATOR CUFF SYNDROME			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL PAIN			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL STENOSIS			
subjects affected / exposed	2 / 324 (0.62%)	2 / 321 (0.62%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPONDYLOLISTHESIS			
subjects affected / exposed	2 / 324 (0.62%)	2 / 321 (0.62%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENOSYNOVITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
VERTEBRAL FORAMINAL STENOSIS			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
VERTEBRAL OSTEOPHYTE			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ARTHRITIS BACTERIAL			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
BONE TUBERCULOSIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
BRONCHITIS VIRAL			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19 PNEUMONIA			
subjects affected / exposed	6 / 324 (1.85%)	2 / 321 (0.62%)	4 / 179 (2.23%)
occurrences causally related to treatment / all	0 / 6	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
CELLULITIS			
subjects affected / exposed	1 / 324 (0.31%)	2 / 321 (0.62%)	0 / 179 (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
CELLULITIS STAPHYLOCOCCAL			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHORIORETINITIS			

subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
COLONIC ABSCESS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
DIVERTICULITIS			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
ENDOCARDITIS STAPHYLOCOCCAL			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
ERYSIPELAS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
EXTRADURAL ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
EXTRAPULMONARY TUBERCULOSIS			
subjects affected / exposed	0 / 324 (0.00%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			

subjects affected / exposed	1 / 324 (0.31%)	2 / 321 (0.62%)	0 / 179 (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
GROIN ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS B REACTIVATION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER CUTANEOUS DISSEMINATED			
subjects affected / exposed	0 / 324 (0.00%)	2 / 321 (0.62%)	0 / 179 (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
INFECTION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ABSCESS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
METAPNEUMOVIRUS INFECTION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
MUSCLE ABSCESS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
NECROTISING FASCIITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PERITONITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
PNEUMONIA			
subjects affected / exposed	6 / 324 (1.85%)	11 / 321 (3.43%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	4 / 6	10 / 13	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PNEUMONIA STREPTOCOCCAL			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
POST PROCEDURAL INFECTION			
subjects affected / exposed	1 / 324 (0.31%)	1 / 321 (0.31%)	0 / 179 (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
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
PYELONEPHRITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
SALPINGO-OOPHORITIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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	1 / 324 (0.31%)	4 / 321 (1.25%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
SIALOADENITIS			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
TONSILLITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBERCULOSIS			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (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
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 324 (0.62%)	2 / 321 (0.62%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICELLA			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
VESTIBULAR NEURONITIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
VIRAL UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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 STAPHYLOCOCCAL			
subjects affected / exposed	0 / 324 (0.00%)	3 / 321 (0.93%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
YERSINIA INFECTION			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
LACTIC ACIDOSIS			
subjects affected / exposed	0 / 324 (0.00%)	1 / 321 (0.31%)	0 / 179 (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
OBESITY			
subjects affected / exposed	1 / 324 (0.31%)	0 / 321 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Period 1: Placebo	Period 1: Upadacitinib 15 mg	Period 1: Upadacitinib 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 221 (30.77%)	83 / 221 (37.56%)	74 / 219 (33.79%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	5 / 221 (2.26%)	1 / 221 (0.45%)	5 / 219 (2.28%)
occurrences (all)	5	1	5
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 221 (2.71%)	2 / 221 (0.90%)	3 / 219 (1.37%)
occurrences (all)	6	2	3
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	0 / 221 (0.00%)	5 / 221 (2.26%)	7 / 219 (3.20%)
occurrences (all)	0	5	7
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 221 (0.45%)	2 / 221 (0.90%)	2 / 219 (0.91%)
occurrences (all)	1	2	3
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	4 / 221 (1.81%)	3 / 221 (1.36%)	2 / 219 (0.91%)
occurrences (all)	4	3	2
Nervous system disorders			
HEADACHE			
subjects affected / exposed	12 / 221 (5.43%)	9 / 221 (4.07%)	8 / 219 (3.65%)
occurrences (all)	14	9	9
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 221 (0.45%)	1 / 221 (0.45%)	2 / 219 (0.91%)
occurrences (all)	1	1	2
LEUKOPENIA			
subjects affected / exposed	1 / 221 (0.45%)	4 / 221 (1.81%)	4 / 219 (1.83%)
occurrences (all)	1	4	4
NEUTROPENIA			
subjects affected / exposed	0 / 221 (0.00%)	4 / 221 (1.81%)	6 / 219 (2.74%)
occurrences (all)	0	4	6
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	2 / 219 (0.91%)
occurrences (all)	0	0	2
Gastrointestinal disorders			

DIARRHOEA			
subjects affected / exposed	9 / 221 (4.07%)	5 / 221 (2.26%)	2 / 219 (0.91%)
occurrences (all)	10	5	2
NAUSEA			
subjects affected / exposed	7 / 221 (3.17%)	15 / 221 (6.79%)	3 / 219 (1.37%)
occurrences (all)	8	17	3
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	2 / 221 (0.90%)	9 / 221 (4.07%)	3 / 219 (1.37%)
occurrences (all)	2	9	3
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	2 / 221 (0.90%)	1 / 221 (0.45%)	5 / 219 (2.28%)
occurrences (all)	2	1	5
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 221 (0.90%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences (all)	2	0	0
BACK PAIN			
subjects affected / exposed	2 / 221 (0.90%)	6 / 221 (2.71%)	2 / 219 (0.91%)
occurrences (all)	2	7	2
RHEUMATOID ARTHRITIS			
subjects affected / exposed	10 / 221 (4.52%)	4 / 221 (1.81%)	4 / 219 (1.83%)
occurrences (all)	11	4	5
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	5 / 221 (2.26%)	4 / 221 (1.81%)	5 / 219 (2.28%)
occurrences (all)	5	4	5
COVID-19			
subjects affected / exposed	0 / 221 (0.00%)	0 / 221 (0.00%)	0 / 219 (0.00%)
occurrences (all)	0	0	0
HERPES ZOSTER			
subjects affected / exposed	1 / 221 (0.45%)	1 / 221 (0.45%)	1 / 219 (0.46%)
occurrences (all)	1	1	1
INFLUENZA			

subjects affected / exposed	2 / 221 (0.90%)	1 / 221 (0.45%)	3 / 219 (1.37%)
occurrences (all)	2	1	3
NASOPHARYNGITIS			
subjects affected / exposed	9 / 221 (4.07%)	12 / 221 (5.43%)	13 / 219 (5.94%)
occurrences (all)	10	13	14
PHARYNGITIS			
subjects affected / exposed	0 / 221 (0.00%)	2 / 221 (0.90%)	2 / 219 (0.91%)
occurrences (all)	0	2	2
SINUSITIS			
subjects affected / exposed	1 / 221 (0.45%)	6 / 221 (2.71%)	1 / 219 (0.46%)
occurrences (all)	1	6	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	9 / 221 (4.07%)	12 / 221 (5.43%)	12 / 219 (5.48%)
occurrences (all)	10	12	13
URINARY TRACT INFECTION			
subjects affected / exposed	8 / 221 (3.62%)	8 / 221 (3.62%)	6 / 219 (2.74%)
occurrences (all)	8	8	6
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	1 / 221 (0.45%)	1 / 221 (0.45%)	2 / 219 (0.91%)
occurrences (all)	1	1	2

Non-serious adverse events	Period 1+2: Upadacitinib 15 mg	Period 1+2: Upadacitinib 30 mg	Period 2: Upadacitinib 15 mg After Switch
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 324 (74.38%)	233 / 321 (72.59%)	51 / 179 (28.49%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	36 / 324 (11.11%)	33 / 321 (10.28%)	2 / 179 (1.12%)
occurrences (all)	42	41	2
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	33 / 324 (10.19%)	25 / 321 (7.79%)	3 / 179 (1.68%)
occurrences (all)	44	31	3
BLOOD CREATINE PHOSPHOKINASE INCREASED			

subjects affected / exposed	36 / 324 (11.11%)	32 / 321 (9.97%)	1 / 179 (0.56%)
occurrences (all)	55	46	1
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	21 / 324 (6.48%)	17 / 321 (5.30%)	5 / 179 (2.79%)
occurrences (all)	28	19	5
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	41 / 324 (12.65%)	27 / 321 (8.41%)	4 / 179 (2.23%)
occurrences (all)	45	29	4
Nervous system disorders			
HEADACHE			
subjects affected / exposed	21 / 324 (6.48%)	21 / 321 (6.54%)	2 / 179 (1.12%)
occurrences (all)	24	24	2
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	20 / 324 (6.17%)	10 / 321 (3.12%)	0 / 179 (0.00%)
occurrences (all)	24	14	0
LEUKOPENIA			
subjects affected / exposed	17 / 324 (5.25%)	20 / 321 (6.23%)	2 / 179 (1.12%)
occurrences (all)	26	34	2
NEUTROPENIA			
subjects affected / exposed	13 / 324 (4.01%)	26 / 321 (8.10%)	3 / 179 (1.68%)
occurrences (all)	21	35	3
General disorders and administration site conditions			
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	18 / 324 (5.56%)	15 / 321 (4.67%)	1 / 179 (0.56%)
occurrences (all)	23	20	2
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	22 / 324 (6.79%)	15 / 321 (4.67%)	0 / 179 (0.00%)
occurrences (all)	24	15	0
NAUSEA			
subjects affected / exposed	30 / 324 (9.26%)	18 / 321 (5.61%)	1 / 179 (0.56%)
occurrences (all)	40	20	1
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	24 / 324 (7.41%)	26 / 321 (8.10%)	0 / 179 (0.00%)
occurrences (all)	28	33	0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	6 / 324 (1.85%)	21 / 321 (6.54%)	2 / 179 (1.12%)
occurrences (all)	7	23	2
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	23 / 324 (7.10%)	10 / 321 (3.12%)	1 / 179 (0.56%)
occurrences (all)	28	10	1
BACK PAIN			
subjects affected / exposed	31 / 324 (9.57%)	21 / 321 (6.54%)	3 / 179 (1.68%)
occurrences (all)	37	22	3
RHEUMATOID ARTHRITIS			
subjects affected / exposed	36 / 324 (11.11%)	30 / 321 (9.35%)	8 / 179 (4.47%)
occurrences (all)	54	41	8
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	35 / 324 (10.80%)	42 / 321 (13.08%)	2 / 179 (1.12%)
occurrences (all)	55	58	2
COVID-19			
subjects affected / exposed	20 / 324 (6.17%)	2 / 321 (0.62%)	16 / 179 (8.94%)
occurrences (all)	21	2	16
HERPES ZOSTER			
subjects affected / exposed	27 / 324 (8.33%)	44 / 321 (13.71%)	4 / 179 (2.23%)
occurrences (all)	29	46	4
INFLUENZA			
subjects affected / exposed	15 / 324 (4.63%)	22 / 321 (6.85%)	0 / 179 (0.00%)
occurrences (all)	18	23	0
NASOPHARYNGITIS			
subjects affected / exposed	60 / 324 (18.52%)	45 / 321 (14.02%)	3 / 179 (1.68%)
occurrences (all)	105	75	3
PHARYNGITIS			
subjects affected / exposed	18 / 324 (5.56%)	9 / 321 (2.80%)	0 / 179 (0.00%)
occurrences (all)	19	10	0

SINUSITIS			
subjects affected / exposed	28 / 324 (8.64%)	22 / 321 (6.85%)	1 / 179 (0.56%)
occurrences (all)	40	23	2
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	64 / 324 (19.75%)	57 / 321 (17.76%)	4 / 179 (2.23%)
occurrences (all)	111	84	5
URINARY TRACT INFECTION			
subjects affected / exposed	55 / 324 (16.98%)	46 / 321 (14.33%)	4 / 179 (2.23%)
occurrences (all)	89	71	4
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	12 / 324 (3.70%)	17 / 321 (5.30%)	0 / 179 (0.00%)
occurrences (all)	12	17	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2015	- Updated the study design to add a blinded long-term extension (Period 2). - Revised inclusion criteria: Clarified requirements for subjects who had been receiving csDMARD therapy prior to study entry. Provided acceptable csDMARDS and dose requirements for inclusion. Modified dose requirement of methotrexate for inclusion. Updated hsCRP value requirement at screening. Updated contraception requirements for females and males. - Added the following exclusion criteria: subjects who are considered inadequate responders to bDMARD therapy; subjects with a history of gastrointestinal (GI) perforation or a history of associated GI diseases; subjects with conditions that could interfere with drug absorption; subjects who have received an organ transplant; and subjects who had clinically relevant or significant electrocardiogram (ECG) abnormalities. - Added an interim data analysis after the completion of Period 1.
01 April 2016	- Addition of CDAI calculation at Week 24 to determine LDA. - Clarified that starting at Week 24, subjects who do not show 20% improvement in tender joint count (TJC) and swollen joint count (SJC) compared to baseline at 2 consecutive visits should discontinue study drug.
31 March 2017	- Revised contraception recommendations for males including sperm donation time frame and clarified follicle-stimulating hormone testing requirements for females. - Added/updated key secondary endpoints, additional endpoints. - Updated statistical sections for accuracy and clarity. - Incorporated Canada and South Korea country-specific requirements.
21 June 2017	- Revised contraception recommendations for females if childbearing potential status changed during the course of the study. - Updated examples of commonly used strong CYP3A inhibitors and inducers, to include rifapentine. - Updated statistical sections for accuracy and clarity.
26 October 2017	- Updated female contraception recommendation language to clarify that injectable hormonal contraception was allowed. Clarified that verbal confirmation of vasectomized partner was an acceptable form of contraception. - Clarified that live vaccines were prohibited up to 30 days following last dose of study drug. - Updated study procedures to prevent unnecessary initiation of tuberculosis (TB) prophylaxis in subject with indeterminate QuantiFERON-TB test results by allowing local testing. - Updated study procedures to prevent unnecessary pregnancy test for women who become post-menopausal or surgically sterile during the study. - Added wording to study procedures for management of subjects with hepatitis B core antibody (Ab)+ (irrespective of hepatitis B surface Ab status) and negative hepatitis B virus DNA at screening and elevated levels of transaminases during study that may indicate active hepatitis which would require hepatitis B virus DNA polymerase chain reaction testing for confirmation. - Clarified a radiologist or pulmonologist may perform assessment of chest x-ray. - Updated the adverse events of special interest (AESI) that was to be monitored during the study to align in content and presentation with the current version of the Product Safety SAP.

16 December 2019	- Changed length of study from 240 weeks to 260 weeks throughout protocol to collect long-term safety data up to 5 years. - Changed dosing for all subjects to 15 mg QD open-label throughout protocol. - Added verbiage to explain that unblinded hsCRP results will be sent to site. - Clarified that restart of study drug after an interruption of > 30 consecutive days is at the discretion of the Investigator. - Clarified concurrent use of JAK inhibitors is prohibited during the study. Updated excluded biologic therapies to be consistent with current available biologic therapies in RA. Added allowance of high potency opiates for analgesic care related to AEs or SAEs. Added guidance for use of live vaccine administration during Period 2. - Removed male contraception requirements. - Provided guidance for interpretation of positive TB testing results in low risk subjects and added the ability to retest locally to confirm central laboratory result as a false-positive result is more likely in low risk subjects. Added use of Interferon Gamma Release Assay as a substitute for local TB testing. Clarification on test method to be used for annual TB testing. Specified that only subjects with newly identified TB risks are subject to chest x-rays. - Added an additional safety precaution for subjects regarding risk of venous thromboembolic events (VTE). - Specified the DMC concluded its oversight of the study after reviewing the unblinded safety data at the end of Period 1. - Updated study drug accountability requirements according to the revised sponsor guidelines. - Clarified throughout Medical Complaints section that all cardiac, embolic and thrombotic events will be adjudicated. - Added herpes zoster and recommendation for skin examination under Toxicity Management and updated AST or ALT parameters for management. - Added text to clarify what happens to optional exploratory research samples in the event a subject withdraws from the main study.
15 July 2020	- Updated allowance for administration of live vaccines during Period 2 with the following guidance: 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). - Clarified that contraception recommendations related to use of background csDMARDs including methotrexate, as well as concomitant therapies prescribed per standard of care, should be based on the local label.
25 November 2020	- Added an evaluation of the benefit and risk to subjects participating in the study relative to COVID-19. - Added provisions for virtual or alternative locations for study visits in the event of a pandemic situation like COVID-19 or any state of emergency to ensure the safety of subjects and site staff, while maintaining the integrity of the study. - Updated list of examples of commonly used strong cytochrome 3A inducers. - Added clarifications on 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, as permitted by IRB/IEC. - Specified activities not eligible for completion by virtual interview in the event that an onsite visit cannot be performed due to a pandemic or state of emergency and should be completed at the next earliest feasible visit. - Added provision allowing Direct-to-Patient (DTP) shipment of study drug and study ancillaries due to state of emergency or pandemic situations. - Clarified that subjects will have to discontinue study drug treatment immediately if they develop a gastrointestinal perforation with the exception of appendicitis or mechanical injury. Added mitigation strategies regarding study discontinuation. - Clarified and updated the list of the adverse events of special interest. - Added supplemental COVID-19 case report forms. - Updated text to define Pregnancy and Product Complaint reporting timeline as 24 hours from site staff awareness. - Added guidance for investigators on the management of subjects with suspected or confirmed COVID-19 infection during the study. - Added option for verbal consent in the event of a pandemic situation. - Clarified that clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices.

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/29908669