



## 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 |
| Global end of trial date | 15 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, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |
| Scientific contact           | Global Medical Services, AbbVie, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |

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     |
| <b>Arm title</b>             | 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.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 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.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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                          |
| <b>Arm title</b>             | 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.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | 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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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 <sup>[1]</sup>   | 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 <sup>[2]</sup>             | 53                           | 0 <sup>[3]</sup>                        |
| 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 <sup>[1]</sup>   | 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."<br>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.<br>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.<br>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  |

|  |       |  |  |
|--|-------|--|--|
| <b>Reporting group values</b>                            | 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)   |   |  |  |
| <p>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.</p> |   |  |  |
| 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])   |   |  |  |
| <p>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.</p>  |   |  |  |
| 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:   |  |
| <p>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 <math>\leq 3.2</math> 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.</p> <p>A DAS28 score less than or equal to 3.2 indicates low disease activity.</p> <p>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.</p> |  |
| 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 <sup>[1]</sup>  | 221 <sup>[2]</sup>  | 219 <sup>[3]</sup>  |  |
| 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 <sup>[4]</sup>          |
| P-value                                 | < 0.001 <sup>[5]</sup>              |
| 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 <sup>[6]</sup>          |
| P-value                                 | < 0.001 <sup>[7]</sup>              |
| 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.

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

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

### 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 <sup>[8]</sup>  | 221 <sup>[9]</sup>  | 219 <sup>[10]</sup> |  |
| 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

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[11]</sup>           |
| P-value                                 | < 0.001 <sup>[12]</sup>               |
| 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.

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[13]</sup>           |
| P-value                                 | < 0.001 <sup>[14]</sup>               |
| 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 <sup>[15]</sup>    | 217 <sup>[16]</sup>    | 219 <sup>[17]</sup>    |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[18]</sup>                     |
| P-value                                 | < 0.001 <sup>[19]</sup>                         |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[20]</sup>                     |
| P-value                                 | < 0.001 <sup>[21]</sup>                         |
| 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:<br>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:<br>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 <sup>[22]</sup>    | 216 <sup>[23]</sup>    | 219 <sup>[24]</sup>    |  |
| 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 <sup>[25]</sup>                |
| P-value                                 | < 0.001 <sup>[26]</sup>                    |
| 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 <sup>[27]</sup>  |
| P-value                                 | < 0.001 <sup>[28]</sup>      |
| 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 <sup>[29]</sup> | 209 <sup>[30]</sup> | 197 <sup>[31]</sup> |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[32]</sup>                   |
| P-value                                 | < 0.001 <sup>[33]</sup>                       |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[34]</sup>                   |
| P-value                                 | < 0.001 <sup>[35]</sup>                       |
| 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:   |   |
| <p>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.</p> <p>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.</p> |   |
| 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 <sup>[36]</sup> | 221 <sup>[37]</sup> | 219 <sup>[38]</sup> |  |
| 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 <sup>[39]</sup>                        |
| P-value                                 | < 0.001 <sup>[40]</sup>                            |
| 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 <sup>[41]</sup>                        |
| P-value                                 | < 0.001 <sup>[42]</sup>                            |
| 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  $\leq 10$ . 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 <sup>[43]</sup> | 221 <sup>[44]</sup> | 219 <sup>[45]</sup> |  |
| 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 <sup>[46]</sup>   |
| P-value                                 | < 0.001 <sup>[47]</sup>       |
| 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.

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[48]</sup>   |
| P-value                                 | < 0.001 <sup>[49]</sup>       |
| 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 <sup>[50]</sup>       | 207 <sup>[51]</sup>        | 197 <sup>[52]</sup>        |  |
| 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

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[53]</sup>             |
| P-value                                 | < 0.001 <sup>[54]</sup>                 |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[55]</sup>             |
| P-value                                 | < 0.001 <sup>[56]</sup>                 |
| 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 <sup>[57]</sup> | 207 <sup>[58]</sup> | 197 <sup>[59]</sup> |  |
| 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 <sup>[60]</sup>           |
| P-value                                 | < 0.001 <sup>[61]</sup>               |
| 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 <sup>[62]</sup>           |
| P-value                                 | < 0.001 <sup>[63]</sup>               |
| 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 <sup>[64]</sup> | 221 <sup>[65]</sup> | 219 <sup>[66]</sup> |  |
| 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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[67]</sup>      |
| 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.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[68]</sup>      |
| 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.  $\geq$  70% improvement in 68-tender joint count;
2.  $\geq$  70% improvement in 66-swollen joint count; and
3.  $\geq$  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 <sup>[69]</sup> | 221 <sup>[70]</sup> | 219 <sup>[71]</sup> |  |
| 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 <sup>[72]</sup>      |
| 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 <sup>[73]</sup>      |
| 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.  $\geq 20\%$  improvement in 68-tender joint count;
2.  $\geq 20\%$  improvement in 66-swollen joint count; and
3.  $\geq 20\%$  improvement in at least 3 of the 5 following parameters:
  - i) Physician global assessment of disease activity;
  - ii) Patient global assessment of disease activity;
  - iii) Patient assessment of pain;
  - iv) Health Assessment Questionnaire - Disability Index (HAQ-DI);
  - v) High-sensitivity C-reactive protein (hsCRP).

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 1

| End point values                  | Placebo             | Upadacitinib 15 mg  | Upadacitinib 30 mg  |  |
|-----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed       | 221 <sup>[74]</sup> | 221 <sup>[75]</sup> | 219 <sup>[76]</sup> |  |
| 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 <sup>[77]</sup>              |
| 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.

|   |                                      |
|---|--------------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[78]</sup>              |
| 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:<br>Upadacitinib 15 mg | Period 1:<br>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)<br>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           |
| <b>HALLUCINATION</b>                            |                 |                 |                 |
| 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>MENTAL STATUS CHANGES</b>                    |                 |                 |                 |
| 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>SUICIDE ATTEMPT</b>                          |                 |                 |                 |
| 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           |
| <b>Product issues</b>                           |                 |                 |                 |
| <b>DEVICE BREAKAGE</b>                          |                 |                 |                 |
| 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>DEVICE MATERIAL ISSUE</b>                    |                 |                 |                 |
| 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>Investigations</b>                           |                 |                 |                 |
| <b>C-REACTIVE PROTEIN INCREASED</b>             |                 |                 |                 |
| 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>GAMMA-GLUTAMYLTRANSFERASE INCREASED</b>      |                 |                 |                 |
| 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           |
| <b>Eye disorders</b>                            |                 |                 |                 |
| <b>CORNEAL DECOMPENSATION</b>                   |                 |                 |                 |
| 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>RETINAL DETACHMENT</b>                       |                 |                 |                 |
| 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>RETINAL TEAR</b>                             |                 |                 |                 |
| 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>ULCERATIVE KERATITIS</b>                     |                 |                 |                 |
| 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>Gastrointestinal disorders</b>               |                 |                 |                 |
| <b>ABDOMINAL PAIN</b>                           |                 |                 |                 |
| 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>ANAL FISSURE</b>                             |                 |                 |                 |
| 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>COLITIS</b>                                  |                 |                 |                 |
| 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>COLITIS ISCHAEMIC</b>                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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                     |                 |                 |                 |
| ABSCCESS 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           |
| <b>BONE TUBERCULOSIS</b>                        |                 |                 |                 |
| 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>BRONCHITIS</b>                               |                 |                 |                 |
| 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>BRONCHITIS VIRAL</b>                         |                 |                 |                 |
| 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>COVID-19</b>                                 |                 |                 |                 |
| 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>COVID-19 PNEUMONIA</b>                       |                 |                 |                 |
| 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>CELLULITIS</b>                               |                 |                 |                 |
| 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>CELLULITIS STAPHYLOCOCCAL</b>                |                 |                 |                 |
| 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>CHORIORETINITIS</b>                          |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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>COLONIC ABSCESS</b>                          |                 |                 |                 |
| 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>DIVERTICULITIS</b>                           |                 |                 |                 |
| 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>ENDOCARDITIS STAPHYLOCOCCAL</b>              |                 |                 |                 |
| 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>ENTEROCOLITIS INFECTIOUS</b>                 |                 |                 |                 |
| 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           |
| <b>ERYSIPELAS</b>                               |                 |                 |                 |
| 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>EXTRADURAL ABSCESS</b>                       |                 |                 |                 |
| 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>EXTRAPULMONARY TUBERCULOSIS</b>              |                 |                 |                 |
| 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>GASTROENTERITIS</b>                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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>GROIN ABSCESS</b>                            |                 |                 |                 |
| 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>HEPATITIS B REACTIVATION</b>                 |                 |                 |                 |
| 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>HERPES ZOSTER</b>                            |                 |                 |                 |
| 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>HERPES ZOSTER CUTANEOUS DISSEMINATED</b>     |                 |                 |                 |
| 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>INFECTION</b>                                |                 |                 |                 |
| 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>INFECTIOUS PLEURAL EFFUSION</b>              |                 |                 |                 |
| 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>INFLUENZA</b>                                |                 |                 |                 |
| 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>LOWER RESPIRATORY TRACT INFECTION</b>        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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>LUNG ABSCESS</b>                             |                 |                 |                 |
| 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>METAPNEUMOVIRUS INFECTION</b>                |                 |                 |                 |
| 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>MUSCLE ABSCESS</b>                           |                 |                 |                 |
| 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>NECROTISING FASCIITIS</b>                    |                 |                 |                 |
| 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>OSTEOMYELITIS</b>                            |                 |                 |                 |
| 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>PERITONITIS</b>                              |                 |                 |                 |
| 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>PNEUMONIA</b>                                |                 |                 |                 |
| 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           |
| <b>PNEUMONIA STREPTOCOCCAL</b>                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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<br>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           |

| <b>Serious adverse events</b>  | Period 1+2:<br>Upadacitinib 15 mg | Period 1+2:<br>Upadacitinib 30 mg | Period 2:<br>Upadacitinib 15 mg<br>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)<br>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           |
| <b>MALIGNANT MELANOMA</b>                       |                 |                 |                 |
| 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           |
| <b>METASTASES TO SPINE</b>                      |                 |                 |                 |
| 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           |
| <b>NON-HODGKIN'S LYMPHOMA STAGE IV</b>          |                 |                 |                 |
| 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           |
| <b>OVARIAN GERM CELL TERATOMA BENIGN</b>        |                 |                 |                 |
| 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           |
| <b>PAPILLARY THYROID CANCER</b>                 |                 |                 |                 |
| 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           |
| <b>PITUITARY TUMOUR BENIGN</b>                  |                 |                 |                 |
| 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           |
| <b>PROSTATE CANCER</b>                          |                 |                 |                 |
| 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           |
| <b>PROSTATE CANCER STAGE II</b>                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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           |
| <b>HALLUCINATION</b>                            |                 |                 |                 |
| 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           |
| <b>MENTAL STATUS CHANGES</b>                    |                 |                 |                 |
| 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           |
| <b>SUICIDE ATTEMPT</b>                          |                 |                 |                 |
| 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           |
| <b>Product issues</b>                           |                 |                 |                 |
| <b>DEVICE BREAKAGE</b>                          |                 |                 |                 |
| 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           |
| <b>DEVICE MATERIAL ISSUE</b>                    |                 |                 |                 |
| 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           |
| <b>Investigations</b>                           |                 |                 |                 |
| <b>C-REACTIVE PROTEIN INCREASED</b>             |                 |                 |                 |
| 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           |
| <b>GAMMA-GLUTAMYLTRANSFERASE INCREASED</b>      |                 |                 |                 |
| 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           |
| COMMUNUTED 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           |
| <b>SYNCOPE</b>                                  |                 |                 |                 |
| 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           |
| <b>TRANSIENT GLOBAL AMNESIA</b>                 |                 |                 |                 |
| 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           |
| <b>TRANSIENT ISCHAEMIC ATTACK</b>               |                 |                 |                 |
| 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           |
| <b>VOCAL CORD PARALYSIS</b>                     |                 |                 |                 |
| 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           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| <b>ANAEMIA</b>                                  |                 |                 |                 |
| 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           |
| <b>ANAEMIA MACROCYTIC</b>                       |                 |                 |                 |
| 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>BLOOD LOSS ANAEMIA</b>                       |                 |                 |                 |
| 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           |
| <b>LYMPHADENITIS</b>                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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           |
| <b>Eye disorders</b>                            |                 |                 |                 |
| <b>CORNEAL DECOMPENSATION</b>                   |                 |                 |                 |
| 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           |
| <b>RETINAL DETACHMENT</b>                       |                 |                 |                 |
| 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           |
| <b>RETINAL TEAR</b>                             |                 |                 |                 |
| 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           |
| <b>ULCERATIVE KERATITIS</b>                     |                 |                 |                 |
| 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           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| <b>ABDOMINAL PAIN</b>                           |                 |                 |                 |
| 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>ANAL FISSURE</b>                             |                 |                 |                 |
| 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           |
| <b>COLITIS</b>                                  |                 |                 |                 |
| 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           |
| <b>COLITIS ISCHAEMIC</b>                        |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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                     |                 |                 |                 |
| ABSCCESS 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           |
| <b>BONE TUBERCULOSIS</b>                        |                 |                 |                 |
| 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           |
| <b>BRONCHITIS</b>                               |                 |                 |                 |
| 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           |
| <b>BRONCHITIS VIRAL</b>                         |                 |                 |                 |
| 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           |
| <b>COVID-19</b>                                 |                 |                 |                 |
| 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           |
| <b>COVID-19 PNEUMONIA</b>                       |                 |                 |                 |
| 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           |
| <b>CELLULITIS</b>                               |                 |                 |                 |
| 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           |
| <b>CELLULITIS STAPHYLOCOCCAL</b>                |                 |                 |                 |
| 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           |
| <b>CHORIORETINITIS</b>                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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           |
| <b>COLONIC ABSCESS</b>                          |                 |                 |                 |
| 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           |
| <b>DIVERTICULITIS</b>                           |                 |                 |                 |
| 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           |
| <b>ENDOCARDITIS STAPHYLOCOCCAL</b>              |                 |                 |                 |
| 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>ENTEROCOLITIS INFECTIOUS</b>                 |                 |                 |                 |
| 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           |
| <b>ERYSIPELAS</b>                               |                 |                 |                 |
| 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           |
| <b>EXTRADURAL ABSCESS</b>                       |                 |                 |                 |
| 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           |
| <b>EXTRAPULMONARY TUBERCULOSIS</b>              |                 |                 |                 |
| 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           |
| <b>GASTROENTERITIS</b>                          |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| 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<br>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:<br>Upadacitinib 15 mg | Period 1:<br>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<br>INCREASED                 |                   |                                 |                                 |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 5 / 221 (2.26%)<br>5   | 1 / 221 (0.45%)<br>1 | 5 / 219 (2.28%)<br>5 |
| ASPARTATE AMINOTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)   | 6 / 221 (2.71%)<br>6   | 2 / 221 (0.90%)<br>2 | 3 / 219 (1.37%)<br>3 |
| BLOOD CREATINE PHOSPHOKINASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)   | 0 / 221 (0.00%)<br>0   | 5 / 221 (2.26%)<br>5 | 7 / 219 (3.20%)<br>7 |
| Injury, poisoning and procedural<br>complications<br>FALL<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 221 (0.45%)<br>1   | 2 / 221 (0.90%)<br>2 | 2 / 219 (0.91%)<br>3 |
| Vascular disorders<br>HYPERTENSION<br>subjects affected / exposed<br>occurrences (all)  | 4 / 221 (1.81%)<br>4   | 3 / 221 (1.36%)<br>3 | 2 / 219 (0.91%)<br>2 |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 12 / 221 (5.43%)<br>14 | 9 / 221 (4.07%)<br>9 | 8 / 219 (3.65%)<br>9 |
| Blood and lymphatic system disorders<br>ANAEMIA<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 221 (0.45%)<br>1   | 1 / 221 (0.45%)<br>1 | 2 / 219 (0.91%)<br>2 |
| LEUKOPENIA<br>subjects affected / exposed<br>occurrences (all)  | 1 / 221 (0.45%)<br>1   | 4 / 221 (1.81%)<br>4 | 4 / 219 (1.83%)<br>4 |
| NEUTROPENIA<br>subjects affected / exposed<br>occurrences (all)   | 0 / 221 (0.00%)<br>0   | 4 / 221 (1.81%)<br>4 | 6 / 219 (2.74%)<br>6 |
| General disorders and administration<br>site conditions<br>INFLUENZA LIKE ILLNESS<br>subjects affected / exposed<br>occurrences (all) | 0 / 221 (0.00%)<br>0   | 0 / 221 (0.00%)<br>0 | 2 / 219 (0.91%)<br>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<br>occurrences (all) | 2 / 221 (0.90%)<br>2  | 1 / 221 (0.45%)<br>1   | 3 / 219 (1.37%)<br>3   |
| <b>NASOPHARYNGITIS</b>                           |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 9 / 221 (4.07%)<br>10 | 12 / 221 (5.43%)<br>13 | 13 / 219 (5.94%)<br>14 |
| <b>PHARYNGITIS</b>                               |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 0 / 221 (0.00%)<br>0  | 2 / 221 (0.90%)<br>2   | 2 / 219 (0.91%)<br>2   |
| <b>SINUSITIS</b>                                 |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 221 (0.45%)<br>1  | 6 / 221 (2.71%)<br>6   | 1 / 219 (0.46%)<br>1   |
| <b>UPPER RESPIRATORY TRACT<br/>INFECTION</b>     |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 9 / 221 (4.07%)<br>10 | 12 / 221 (5.43%)<br>12 | 12 / 219 (5.48%)<br>13 |
| <b>URINARY TRACT INFECTION</b>                   |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 8 / 221 (3.62%)<br>8  | 8 / 221 (3.62%)<br>8   | 6 / 219 (2.74%)<br>6   |
| <b>Metabolism and nutrition disorders</b>        |                       |                        |                        |
| <b>HYPERCHOLESTEROLAEMIA</b>                     |                       |                        |                        |
| subjects affected / exposed<br>occurrences (all) | 1 / 221 (0.45%)<br>1  | 1 / 221 (0.45%)<br>1   | 2 / 219 (0.91%)<br>2   |

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



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

|   |   |  |  |
|---|---|--|--|
| COUGH<br>subjects affected / exposed<br>occurrences (all)   | 24 / 324 (7.41%)<br>28  | 26 / 321 (8.10%)<br>33   | 0 / 179 (0.00%)<br>0   |
| Skin and subcutaneous tissue disorders<br>RASH<br>subjects affected / exposed<br>occurrences (all)  | 6 / 324 (1.85%)<br>7  | 21 / 321 (6.54%)<br>23   | 2 / 179 (1.12%)<br>2   |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)<br><br>BACK PAIN<br>subjects affected / exposed<br>occurrences (all)<br><br>RHEUMATOID ARTHRITIS<br>subjects affected / exposed<br>occurrences (all)  | 23 / 324 (7.10%)<br>28<br><br>31 / 324 (9.57%)<br>37<br><br>36 / 324 (11.11%)<br>54   | 10 / 321 (3.12%)<br>10<br><br>21 / 321 (6.54%)<br>22<br><br>30 / 321 (9.35%)<br>41   | 1 / 179 (0.56%)<br>1<br><br>3 / 179 (1.68%)<br>3<br><br>8 / 179 (4.47%)<br>8   |
| Infections and infestations<br>BRONCHITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>COVID-19<br>subjects affected / exposed<br>occurrences (all)<br><br>HERPES ZOSTER<br>subjects affected / exposed<br>occurrences (all)<br><br>INFLUENZA<br>subjects affected / exposed<br>occurrences (all)<br><br>NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>PHARYNGITIS<br>subjects affected / exposed<br>occurrences (all) | 35 / 324 (10.80%)<br>55<br><br>20 / 324 (6.17%)<br>21<br><br>27 / 324 (8.33%)<br>29<br><br>15 / 324 (4.63%)<br>18<br><br>60 / 324 (18.52%)<br>105<br><br>18 / 324 (5.56%)<br>19 | 42 / 321 (13.08%)<br>58<br><br>2 / 321 (0.62%)<br>2<br><br>44 / 321 (13.71%)<br>46<br><br>22 / 321 (6.85%)<br>23<br><br>45 / 321 (14.02%)<br>75<br><br>9 / 321 (2.80%)<br>10 | 2 / 179 (1.12%)<br>2<br><br>16 / 179 (8.94%)<br>16<br><br>4 / 179 (2.23%)<br>4<br><br>0 / 179 (0.00%)<br>0<br><br>3 / 179 (1.68%)<br>3<br><br>0 / 179 (0.00%)<br>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 | <ul style="list-style-type: none"><li>- Updated the study design to add a blinded long-term extension (Period 2).</li><li>- 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.</li><li>- 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.</li><li>- Added an interim data analysis after the completion of Period 1.</li></ul>  |
| 01 April 2016    | <ul style="list-style-type: none"><li>- Addition of CDAI calculation at Week 24 to determine LDA.</li><li>- 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.</li></ul>   |
| 31 March 2017    | <ul style="list-style-type: none"><li>- Revised contraception recommendations for males including sperm donation time frame and clarified follicle-stimulating hormone testing requirements for females.</li><li>- Added/updated key secondary endpoints, additional endpoints.</li><li>- Updated statistical sections for accuracy and clarity.</li><li>- Incorporated Canada and South Korea country-specific requirements.</li></ul>  |
| 21 June 2017     | <ul style="list-style-type: none"><li>- Revised contraception recommendations for females if childbearing potential status changed during the course of the study.</li><li>- Updated examples of commonly used strong CYP3A inhibitors and inducers, to include rifapentine.</li><li>- Updated statistical sections for accuracy and clarity.</li></ul>  |
| 26 October 2017  | <ul style="list-style-type: none"><li>- 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.</li><li>- Clarified that live vaccines were prohibited up to 30 days following last dose of study drug.</li><li>- Updated study procedures to prevent unnecessary initiation of tuberculosis (TB) prophylaxis in subject with indeterminate QuantiFERON-TB test results by allowing local testing.</li><li>- Updated study procedures to prevent unnecessary pregnancy test for women who become post-menopausal or surgically sterile during the study.</li><li>- 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.</li><li>- Clarified a radiologist or pulmonologist may perform assessment of chest x-ray.</li><li>- 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.</li></ul> |

|                  |  |
|------------------|--|
| 16 December 2019 | <ul style="list-style-type: none"> <li>- Changed length of study from 240 weeks to 260 weeks throughout protocol to collect long-term safety data up to 5 years.</li> <li>- Changed dosing for all subjects to 15 mg QD open-label throughout protocol.</li> <li>- Added verbiage to explain that unblinded hsCRP results will be sent to site.</li> <li>- Clarified that restart of study drug after an interruption of &gt; 30 consecutive days is at the discretion of the Investigator.</li> <li>- 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.</li> <li>- Removed male contraception requirements.</li> <li>- 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.</li> </ul> <p>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.</p> <ul style="list-style-type: none"> <li>- Added an additional safety precaution for subjects regarding risk of venous thromboembolic events (VTE).</li> <li>- Specified the DMC concluded its oversight of the study after reviewing the unblinded safety data at the end of Period 1.</li> <li>- Updated study drug accountability requirements according to the revised sponsor guidelines.</li> <li>- Clarified throughout Medical Complaints section that all cardiac, embolic and thrombotic events will be adjudicated.</li> <li>- Added herpes zoster and recommendation for skin examination under Toxicity Management and updated AST or ALT parameters for management.</li> <li>- Added text to clarify what happens to optional exploratory research samples in the event a subject withdraws from the main study.</li> </ul> |
| 15 July 2020     | <ul style="list-style-type: none"> <li>- 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).</li> <li>- 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.</li> </ul>  |
| 25 November 2020 | <ul style="list-style-type: none"> <li>- Added an evaluation of the benefit and risk to subjects participating in the study relative to COVID-19.</li> <li>- 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.</li> <li>- Updated list of examples of commonly used strong cytochrome 3A inducers.</li> <li>- 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.</li> <li>- 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.</li> <li>- Added provision allowing Direct-to-Patient (DTP) shipment of study drug and study ancillaries due to state of emergency or pandemic situations.</li> <li>- 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.</li> <li>- Clarified and updated the list of the adverse events of special interest.</li> <li>- Added supplemental COVID-19 case report forms.</li> <li>- Updated text to define Pregnancy and Product Complaint reporting timeline as 24 hours from site staff awareness.</li> <li>- Added guidance for investigators on the management of subjects with suspected or confirmed COVID-19 infection during the study.</li> <li>- Added option for verbal consent in the event of a pandemic situation.</li> <li>- 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.</li> </ul>                             |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported

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### **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/29908669>