



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M13-542 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

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

Protection of trial subjects:

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

Background therapy:

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

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 15 March 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 363 |
| From 65 to 84 years | 135 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

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

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

Dosage and administration details:

Matching placebo tablet

| | |
|------------------|--------------------|
| Arm title | Upadacitinib 15 mg |
|------------------|--------------------|

Arm description:

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

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

Dosage and administration details:

Tablet for oral administration

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

Dosage and administration details:

Tablet for oral administration

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

Notes:

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

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

Period 2

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

Tablet for oral administration

| | |
|------------------|------------------------------|
| Arm title | Placebo / Upadacitinib 30 mg |
|------------------|------------------------------|

Arm description:

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

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

Dosage and administration details:

Tablet for oral administration

| | |
|------------------|--------------------|
| Arm title | Upadacitinib 15 mg |
|------------------|--------------------|

Arm description:

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

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

Dosage and administration details:

Tablet for oral administration

| | |
|------------------|--------------------|
| Arm title | Upadacitinib 30 mg |
|------------------|--------------------|

Arm description:

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

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

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

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

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

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

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

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

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

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

Baseline characteristics

Reporting groups

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

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

| | | | |
|--|---------|---------|---------|
| Asia | 0 | 0 | 1 |
| Other | 3 | 1 | 1 |
| Prior Failed Biological Disease-modifying Anti-rheumatic Drugs (bDMARDs) | | | |
| Randomization was stratified by the number of previous bDMARDs used: Stratum 1 consisted of participants who had inadequate response or intolerance to one or two biologics of the same class; Stratum 2 consisted of participants who had inadequate response or intolerance to at least three biologics of the same class and/or at least two biologics with different mechanisms of action. | | | |
| Units: Subjects | | | |
| Stratum 1 | 117 | 116 | 111 |
| Stratum 2 | 52 | 48 | 54 |
| Concomitant Conventional Synthetic DMARD Use at Baseline | | | |
| Units: Subjects | | | |
| Methotrexate alone | 122 | 118 | 124 |
| Methotrexate and other csDMARD | 17 | 19 | 11 |
| csDMARD other than methotrexate | 29 | 24 | 29 |
| Missing | 1 | 3 | 1 |
| Duration of RA Diagnosis | | | |
| Units: years | | | |
| arithmetic mean | 14.5 | 12.4 | 12.7 |
| standard deviation | ± 9.22 | ± 9.38 | ± 9.65 |
| Tender Joint Count | | | |
| A total of 68 joints were assessed for the presence or absence of tenderness. | | | |
| Units: joints | | | |
| arithmetic mean | 28.5 | 27.8 | 27.3 |
| standard deviation | ± 15.27 | ± 16.31 | ± 15.23 |
| Swollen Joint Count | | | |
| A total of 66 joints were assessed for the presence or absence of swelling. | | | |
| Units: joints | | | |
| arithmetic mean | 16.3 | 17.0 | 17.2 |
| standard deviation | ± 9.58 | ± 10.75 | ± 11.37 |
| Patient's Assessment of Pain | | | |
| Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale (VAS) from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." There were 166 participants, 163 participants, and 161 participants with available data in each treatment group, respectively. | | | |
| Units: mm | | | |
| arithmetic mean | 68.9 | 68.2 | 65.3 |
| standard deviation | ± 21.03 | ± 19.77 | ± 20.67 |
| Patient's Global Assessment of Disease Activity | | | |
| The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 166 participants, 163 participants, and 163 participants with available data in each treatment group, respectively. | | | |
| Units: mm | | | |
| arithmetic mean | 66.3 | 67.2 | 64.7 |
| standard deviation | ± 22.72 | ± 19.60 | ± 21.05 |
| Physician's Global Assessment of Disease Activity | | | |
| The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 161 participants, 157 participants, and 157 participants with available data in each | | | |

| | | | |
|--|---------|---------|---------|
| treatment group, respectively. | | | |
| Units: mm | | | |
| arithmetic mean | 66.9 | 68.7 | 66.4 |
| standard deviation | ± 16.92 | ± 16.59 | ± 15.63 |
| Health Assessment Questionnaire - Disability Index (HAQ-DI) | | | |
| <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).</p> <p>There were 166, 163, and 161 participants with available data in each treatment group, respectively.</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | 1.6 | 1.7 | 1.6 |
| standard deviation | ± 0.60 | ± 0.64 | ± 0.59 |
| High-sensitivity C-reactive Protein (hsCRP) | | | |
| Units: mg/L | | | |
| arithmetic mean | 16.3 | 16.2 | 16.0 |
| standard deviation | ± 21.10 | ± 18.62 | ± 21.23 |
| Disease Activity Score 28 Based on CRP (DAS28[CRP]) | | | |
| <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.</p> <p>There were 166, 163, and 163 participants with available data in each treatment group, respectively.</p> | | | |
| Units: units on a scale | | | |
| arithmetic mean | 5.8 | 5.9 | 5.8 |
| standard deviation | ± 1.00 | ± 0.95 | ± 0.89 |

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

| | | | |
|--|-----|--|--|
| Native Hawaiian or other Pacific Islander | 1 | | |
| Asian | 9 | | |
| Geographic Region | | | |
| Other includes Australia, New Zealand, and Israel. | | | |
| Units: Subjects | | | |
| North America | 328 | | |
| Western Europe | 97 | | |
| Eastern Europe | 67 | | |
| Asia | 1 | | |
| Other | 5 | | |
| Prior Failed Biological Disease-modifying Anti-rheumatic Drugs (bDMARDs) | | | |
| Randomization was stratified by the number of previous bDMARDs used: Stratum 1 consisted of participants who had inadequate response or intolerance to one or two biologics of the same class; Stratum 2 consisted of participants who had inadequate response or intolerance to at least three biologics of the same class and/or at least two biologics with different mechanisms of action. | | | |
| Units: Subjects | | | |
| Stratum 1 | 344 | | |
| Stratum 2 | 154 | | |
| Concomitant Conventional Synthetic DMARD Use at Baseline | | | |
| Units: Subjects | | | |
| Methotrexate alone | 364 | | |
| Methotrexate and other csDMARD | 47 | | |
| csDMARD other than methotrexate | 82 | | |
| Missing | 5 | | |
| Duration of RA Diagnosis | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Tender Joint Count | | | |
| A total of 68 joints were assessed for the presence or absence of tenderness. | | | |
| Units: joints | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Swollen Joint Count | | | |
| A total of 66 joints were assessed for the presence or absence of swelling. | | | |
| Units: joints | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Patient's Assessment of Pain | | | |
| Participants were asked to indicate the severity of their arthritis pain within the previous week on a visual analog scale (VAS) from 0 to 100 mm. A score of 0 mm indicates "no pain" and a score of 100 mm indicates "worst possible pain." There were 166 participants, 163 participants, and 161 participants with available data in each treatment group, respectively. | | | |
| Units: mm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Patient's Global Assessment of Disease Activity | | | |
| The participant was asked to rate their current RA disease activity over the past 24 hours on a 100 mm VAS, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity. There were 166 participants, 163 participants, and 163 participants with available data in each | | | |

| | | | |
|--|---|--|--|
| treatment group, respectively. | | | |
| Units: mm arithmetic mean standard deviation | - | | |
| Physician's Global Assessment of Disease Activity | | | |
| <p>The physician rated the participant's current global RA disease activity (independently from the participant's assessment) on a VAS scale from 0 to 100 mm, where 0 mm indicates very low disease activity and 100 mm indicates very high disease activity.</p> <p>There were 161 participants, 157 participants, and 157 participants with available data in each treatment group, respectively.</p> | | | |
| Units: mm 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).</p> <p>There were 166, 163, and 161 participants 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 28 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.</p> <p>There were 166, 163, and 163 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 randomised to receive placebo once daily for 12 weeks. At Week 12 participants were switched to either upadacitinib 15 mg or upadacitinib 30 mg according to the original randomisation scheme. | |
| Reporting group title | Upadacitinib 15 mg |
| Reporting group description: Participants randomized to receive upadacitinib 15 mg once daily for 12 weeks followed by upadacitinib 15 mg once daily from Week 12 to Week 24. | |
| Reporting group title | Upadacitinib 30 mg |
| Reporting group description: Participants randomized to receive upadacitinib 30 mg once daily for 12 weeks followed by upadacitinib 30 mg once daily from Week 12 to Week 24. | |
| Reporting group title | Placebo / Upadacitinib 15 mg |
| Reporting group description: Participants originally randomized to placebo then upadacitinib 15 mg received upadacitinib 15 mg once daily from Week 24 to Week 260. | |
| Reporting group title | Placebo / Upadacitinib 30 mg |
| Reporting group description: Participants originally randomized to placebo then upadacitinib 30 mg received upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg. | |
| Reporting group title | Upadacitinib 15 mg |
| Reporting group description: Participants originally randomized to receive upadacitinib 15 mg continued to receive upadacitinib 15 mg once daily from Week 24 to Week 260. | |
| Reporting group title | Upadacitinib 30 mg |
| Reporting group description: Participants originally randomized to receive upadacitinib 30 mg continued to receive upadacitinib 30 mg once daily from Week 24 to Week 260. After Protocol Amendment 4 participants still on study were switched to receive upadacitinib 15 mg. | |

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

| | |
|---|--|
| End point title | Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28(CRP) at Week 12 |
| End point description: The primary endpoint for European Union (EU)/European Medicines Agency (EMA) regulatory purposes was low disease activity, based on a Disease Activity Score 28 (DAS28)-CRP score of ≤ 3.2 at Week 12. The DAS28 is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity. A DAS28 score less than or equal to 3.2 indicates low disease activity. The full analysis set (FAS) included all randomized participants who received at least 1 dose of study drug. Participants who prematurely discontinued from study drug prior to Week 12 or for whom DAS28 data were missing at Week 12 were considered non-responders. | |
| End point type | Primary |
| End point timeframe: Week 12 | |

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

Notes:

[1] - Full analysis set

[2] - Full analysis set

[3] - Full analysis set

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

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

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

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 | 169 ^[8] | 164 ^[9] | 165 ^[10] | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 28.4 (21.6 to 35.2) | 64.6 (57.3 to 72.0) | 56.4 (48.8 to 63.9) | |

Notes:

[8] - Full analysis set

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

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

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

Notes:

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

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

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

Notes:

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

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

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

| | |
|-----------------|---|
| End point title | Change From Baseline in in Disease Activity Score 28 (CRP) at Week 12 |
|-----------------|---|

End point description:

The DAS28 is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 range from 0 to approximately 10, where higher scores indicate more disease activity. A negative change from baseline in DAS28 (CRP) indicates improvement in disease activity. Multiple imputation was used for missing data in this analysis.

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

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

Notes:

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

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

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

stratum 2) and baseline value as covariates.

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

| | |
|---|--|
| End point title | Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12 |
| End point description: | |
| <p>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.</p> <p>A negative change from Baseline in the overall score indicates improvement.</p> <p>Multiple imputation was used for missing data in this analysis.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Week 12 | |

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

Notes:

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

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

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

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

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

End point description:

The Short Form 36-Item Health Survey (SF-36) Version 2 is a self-administered questionnaire that measures the impact of disease on overall quality of life during the past 4 weeks. The SF-36 consists of 36 questions in eight domains (physical function, pain, general and mental health, vitality, social function, physical and emotional health).

The physical component score is a weighted combination of the 8 subscales with positive weighting for physical functioning, role-physical, bodily pain, and general health. The PCS was calculated using norm-based scoring so that 50 is the average score and the standard deviation equals 10. Higher scores are associated with better functioning/quality of life; a positive change from baseline score indicates an improvement.

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

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

End point timeframe:

Baseline and Week 12

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

Notes:

[29] - Full analysis set participants with available data

[30] - Full analysis set participants with available data

[31] - Full analysis set participants with available data

Statistical analyses

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

Notes:

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

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

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

Notes:

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

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

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

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

End point description:

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

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

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

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

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

Notes:

[36] - Full analysis set

[37] - Full analysis set

[38] - Full analysis set

Statistical analyses

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

Notes:

[39] - The nominal p-value is reported

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

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

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

Notes:

[41] - The nominal p-value is reported

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

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

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

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 | 169 ^[43] | 164 ^[44] | 165 ^[45] | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 6.5 (2.8 to 10.2) | 11.6 (6.7 to 16.5) | 23.0 (16.6 to 29.5) | |

Notes:

[43] - Full analysis set

[44] - Full analysis set

[45] - Full analysis set

Statistical analyses

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

Notes:

[46] - The nominal p-value is reported

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

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

Notes:

[48] - The nominal p-value is reported

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

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

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

End point description:

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

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

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

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

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

Notes:

[50] - Full analysis set

[51] - Full analysis set

[52] - Full analysis set

Statistical analyses

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

Notes:

[53] - The nominal p-value is reported

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

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

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

Notes:

[55] - The nominal p-value is reported

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Participants received placebo once daily for 12 weeks.

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

Participants received upadacitinib 15 mg once daily for 12 weeks.

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

Participants received upadacitinib 30 mg once daily for 12 weeks.

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

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ADENOCARCINOMA PANCREAS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BASAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BLADDER CANCER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BREAST CANCER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLON CANCER METASTATIC | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENDOMETRIAL ADENOCARCINOMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOLLICULAR THYROID CANCER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMANGIOMA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALIGNANT MELANOMA IN SITU | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NON-SMALL CELL LUNG CANCER METASTATIC | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATIC CARCINOMA STAGE IV | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PROSTATE CANCER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 2 / 165 (1.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RECTAL CANCER METASTATIC | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UTERINE LEIOMYOMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| AORTIC STENOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEEP VEIN THROMBOSIS | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMATOMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTENSION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MAY-THURNER SYNDROME | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PELVIC VENOUS THROMBOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUPERFICIAL VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| ABORTION SPONTANEOUS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| CHEST PAIN | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEATH | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FATIGUE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALAISE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MULTIPLE ORGAN DYSFUNCTION SYNDROME | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUDDEN CARDIAC DEATH | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYSTEMIC INFLAMMATORY RESPONSE SYNDROME | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| GENITAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UTERINE POLYP | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VAGINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ASTHMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHRONIC OBSTRUCTIVE PULMONARY DISEASE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSпноEA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOXIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NASAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY ARREST | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY FAILURE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOCAL CORD POLYP | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| ACUTE PSYCHOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANXIETY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEPRESSION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device material issue | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device pacing issue | | | |

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

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTENTIONAL OVERDOSE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MENISCUS INJURY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POST PROCEDURAL FEVER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ROAD TRAFFIC ACCIDENT | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKIN ABRASION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL COLUMN INJURY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL COMPRESSION FRACTURE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TENDON RUPTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THORACIC VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ULNA FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WOUND | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANGINA UNSTABLE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATRIAL TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FIBRILLATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CORONARY ARTERY DISEASE | | | |

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

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOSS OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LUMBAR RADICULOPATHY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MYELOPATHY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL CLAUDICATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPONDYLITIC MYELOPATHY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TRANSIENT ISCHAEMIC ATTACK | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| VERTIGO | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLITIS ISCHAEMIC | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIVERTICULAR PERFORATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTERITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARGE INTESTINE PERFORATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NAUSEA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATITIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERITONEAL HAEMATOMA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOLVULUS OF SMALL BOWEL | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLESTASIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GALLBLADDER POLYP | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| DIABETIC FOOT | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HIDRADENITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| END STAGE RENAL DISEASE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STRESS URINARY INCONTINENCE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URETEROLITHIASIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| THYROID CYST | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Musculoskeletal and connective tissue disorders | | | |
| ANKLE DEFORMITY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ARTHRALGIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ARTHRITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BURSITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CERVICAL SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EXOSTOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOOT DEFORMITY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|---|-----------------|-----------------|-----------------|--|
| FRACTURE DELAYED UNION | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC DEGENERATION | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC PROTRUSION | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| LUMBAR SPINAL STENOSIS | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| MUSCULAR WEAKNESS | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| OSTEOARTHRITIS | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| RHABDOMYOLYSIS | | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| RHEUMATOID ARTHRITIS | | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPONDYLOLISTHESIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNOVIAL CYST | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| ABDOMINAL ABSCESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| APPENDICITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ASPERGILLUS INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 PNEUMONIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CAVERNOUS SINUS THROMBOSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CELLULITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHEST WALL ABSCESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHRONIC SINUSITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ESCHERICHIA BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ESCHERICHIA INFECTION | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOURNIER'S GANGRENE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS VIRAL | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HERPES ZOSTER CUTANEOUS DISSEMINATED | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFECTED DERMAL CYST | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFLUENZA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OPHTHALMIC HERPES ZOSTER | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 1 / 165 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PELVIC INFLAMMATORY DISEASE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERINEPHRIC ABSCESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 2 / 165 (1.21%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA INFLUENZAL | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POST PROCEDURAL INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POSTOPERATIVE WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION VIRAL | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SINUSITIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SINUSITIS ASPERGILLUS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UROSEPSIS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 1 / 164 (0.61%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VULVAL ABSCESS | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ELECTROLYTE IMBALANCE | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPONATRAEMIA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOVOLAEMIA | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OBESITY | | | |
| subjects affected / exposed | 0 / 169 (0.00%) | 0 / 164 (0.00%) | 0 / 165 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 236 (0.00%) | 1 / 240 (0.42%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 236 (0.42%) | 0 / 240 (0.00%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARGE INTESTINE PERFORATION | | | |
| subjects affected / exposed | 0 / 236 (0.00%) | 1 / 240 (0.42%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NAUSEA | | | |
| subjects affected / exposed | 0 / 236 (0.00%) | 1 / 240 (0.42%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATITIS | | | |
| subjects affected / exposed | 1 / 236 (0.42%) | 0 / 240 (0.00%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERITONEAL HAEMATOMA | | | |
| subjects affected / exposed | 1 / 236 (0.42%) | 0 / 240 (0.00%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 2 / 236 (0.85%) | 0 / 240 (0.00%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOLVULUS OF SMALL BOWEL | | | |
| subjects affected / exposed | 1 / 236 (0.42%) | 0 / 240 (0.00%) | 0 / 138 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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