



Clinical trial results:

A national phase IIIb, multi-center, open label study for women and men with hormone-receptor positive, HER2-negative locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole RIBECCA RIBociclib for the treatment of advanced breast Cancer

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-002556-24 |
| Trial protocol | DE |
| Global end of trial date | 06 February 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 30 August 2021 |
| First version publication date | 22 February 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLEE011XDE01 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03096847 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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 | 06 February 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was the assessment of the clinical benefit rate (CBR) after 24 weeks for the total population and for cohorts A and B separately:

-To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole among postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior treatment for advanced disease. (70% group) (Cohort A)

-To assess the CBR after 24 weeks for ribociclib (LEE011) in combination with letrozole and goserelin among pre-, and perimenopausal women who received no prior treatment for advanced disease as well as pre-, peri- and postmenopausal women and men with hormone receptor positive, HER2- negative, advanced breast cancer who received no more than 1 prior chemotherapy and 2 prior lines of endocrine therapy for advanced disease (30% group) (Cohort B)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 24 October 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 502 |
| Worldwide total number of subjects | 502 |
| EEA total number of subjects | 502 |

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) | 256 |
| From 65 to 84 years | 240 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

504 part. entered study, but 2 of these participants were not treated. The full analysis set (FAS) is comprised of 504 part. minus 17 participants, whose data were removed because of inspection findings, to equal 487 part. This FAS includes 2 part. who entered the study but were not treated.

502 part. were treated and included in the safety set.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ribociclib + letrozole cohort A |

Arm description:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ribociclib |
| Investigational medicinal product code | Ribociclib (LEE011) |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

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

Dosage and administration details:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

| | |
|------------------|----------------------------------|
| Arm title | ribociclib + letrozole cohort B1 |
|------------------|----------------------------------|

Arm description:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ribociclib |
| Investigational medicinal product code | Ribociclib (LEE011) |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|--|--|
| Investigational medicinal product name | Goserelin (for premenopausal patients) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|------------------|----------------------------------|
| Arm title | ribociclib + letrozole cohort B2 |
|------------------|----------------------------------|

Arm description:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ribociclib |
| Investigational medicinal product code | Ribociclib (LEE011) |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|--|--|
| Investigational medicinal product name | Goserelin (for premenopausal patients) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

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

Dosage and administration details:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| Number of subjects in period 1 | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 |
|---------------------------------------|---------------------------------|----------------------------------|----------------------------------|
| Started | 319 | 26 | 157 |
| Full Analysis Set | 307 | 26 | 154 |
| Completed | 100 | 6 | 19 |
| Not completed | 219 | 20 | 138 |
| Adverse event, serious fatal | 6 | - | 2 |
| Physician decision | 12 | 2 | 8 |
| Consent withdrawn by subject | 24 | 1 | 12 |
| Adverse event, non-fatal | 72 | 6 | 28 |
| Non-compliance with study medication | 1 | - | - |
| Lost to follow-up | 1 | - | 1 |
| Progressive disease | 97 | 10 | 78 |
| New therapy for study indication | 1 | - | 1 |
| Protocol deviation | 3 | - | 6 |
| not specified | 2 | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------------------|
| Reporting group title | ribociclib + letrozole cohort A |
| Reporting group description: postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. | |
| Reporting group title | ribociclib + letrozole cohort B1 |
| Reporting group description: premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly | |
| Reporting group title | ribociclib + letrozole cohort B2 |
| Reporting group description: premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly | |

| Reporting group values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 |
|---|---------------------------------|----------------------------------|----------------------------------|
| Number of subjects | 319 | 26 | 157 |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 143 | 26 | 87 |
| >=65 years | 176 | 0 | 70 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 65.7 | 46.5 | 62.8 |
| standard deviation | ± 10.1 | ± 4.9 | ± 12.8 |
| Sex: Female, Male Units: Participants | | | |
| Female | 315 | 26 | 156 |
| Male | 4 | 0 | 1 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 0 |
| White | 312 | 24 | 151 |
| More than one race | 1 | 0 | 3 |
| Unknown or Not Reported | 6 | 0 | 2 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 502 | | |
| Age Categorical Units: Participants | | | |
| <=18 years | 0 | | |
| Between 18 and 65 years | 256 | | |

| | | | |
|------------|-----|--|--|
| >=65 years | 246 | | |
|------------|-----|--|--|

| | | | |
|---|-----|--|--|
| Age Continuous Units: Years arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: Participants | | | |
| Female | 497 | | |
| Male | 5 | | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 2 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 1 | | |
| White | 487 | | |
| More than one race | 4 | | |
| Unknown or Not Reported | 8 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | ribociclib + letrozole cohort A |
|-----------------------|---------------------------------|

Reporting group description:

postmenopausal women, or men; naïve. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily.

| | |
|-----------------------|----------------------------------|
| Reporting group title | ribociclib + letrozole cohort B1 |
|-----------------------|----------------------------------|

Reporting group description:

premenopausal women or perimenopausal women; naïve All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|-----------------------|----------------------------------|
| Reporting group title | ribociclib + letrozole cohort B2 |
|-----------------------|----------------------------------|

Reporting group description:

premenopausal women or perimenopausal women or postmenopausal women, or men; pre-treated. All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o. daily. Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|----------------------------|-------|
| Subject analysis set title | Total |
|----------------------------|-------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Cohort A and Cohort B combined

| | |
|----------------------------|---------------------------------|
| Subject analysis set title | ribociclib + letrozole cohort B |
|----------------------------|---------------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

premenopausal women or perimenopausal women or postmenopausal women, or men; naïve + pre-treated

All patients received ribociclib 600mg p.o. daily + Letrozole 2.5 mg p.o.daily.

Premenopausal patients additionally received goserelin 3.6 mg i.m. monthly

| | |
|----------------------------|-------|
| Subject analysis set title | Total |
|----------------------------|-------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Cohorts A, B1 and B2 combined

| | |
|----------------------------|-------|
| Subject analysis set title | Total |
|----------------------------|-------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Cohort A and Cohort B combined

Primary: Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole

| | |
|-----------------|--|
| End point title | Clinical Benefit Rate (CBR) in women and men with hormone receptor positiv, HER-2 negative breast cancer treated with ribocilib and letrozole ^[1] |
|-----------------|--|

End point description:

Clinical Benefit Rate (CBR) after 24 weeks of treatment as defined by RECIST 1.1 as percentage of patients with Complete Response (CR), Partial response (PR) or Stable disease (SD) lasting 24 weeks or longer as well as patients with Non-complete response, nonprogressive disease (NCRNPD).

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

End point timeframe:

At 24 weeks after last patient enrolled in trial

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Please note that the statistical significance test (test comparing groups) i.e., statistical

analysis was not applicable for this outcome measure, since the primary objective was to assess the rate (per cohort) and not to compare two or more treatment arms, as this was a non-randomized, single arm open label trial.

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | Total |
|------------------------------------|---------------------------------------|--|--|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 307 | 26 | 154 | 487 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| CBR by week 24(Confirmed (BOR)) | 63.2 (57.5 to 68.6) | 57.7 (36.9 to 76.6) | 56.5 (48.3 to 64.5) | 60.8 (56.3 to 65.1) |
| CBR by week 24 (non-confirmed BOR) | 71.7 (66.3 to 76.6) | 69.2 (48.2 to 85.7) | 64.3 (56.2 to 71.8) | 69.2 (64.9 to 73.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) for different populations - Kaplan-Meier estimates (% , 95% CI)

| | |
|------------------------|---|
| End point title | Progression free survival (PFS) for different populations - Kaplan-Meier estimates (% , 95% CI) |
| End point description: | PFS based on radiologic assessment by investigator using RECIST 1.1 criteria |
| End point type | Secondary |
| End point timeframe: | At week 24 , week 48 and week 72 |

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|---|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimates (% , 95% CI) - Week 24 | 73.1 (67.3 to 77.9) | 67.0 (44.7 to 82.0) | 63.8 (55.2 to 71.3) | |
| Kaplan-Meier estimates (% , 95% CI) - Week 48 | 61.9 (55.7 to 67.5) | 58.7 (36.8 to 75.2) | 47.5 (38.7 to 55.7) | |
| Kaplan-Meier estimates (% , 95% CI) - week 72 | 54.5 (48.1 to 60.5) | 49.6 (28.6 to 67.6) | 39.3 (30.8 to 47.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months]

| | |
|--|--|
| End point title | Progression free survival (PFS) for different populations - Median time to progression or death with 95% CI [months] |
| End point description: PFS based on radiologic assessment by investigator using RECIST 1.1 criteria | |
| End point type | Secondary |
| End point timeframe: Up to approximately month 25 | |

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 21.8 (13.9 to 25.3) | 16.5 (3.2 to 999) | 8.8 (8.1 to 16.3) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Kaplan-Meier estimates (% , 95% CI)

| | |
|--|---|
| End point title | Overall Survival (OS) - Kaplan-Meier estimates (% , 95% CI) |
| End point description: Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause. For the Kaplan-Meier estimates (% , 95% CI), the probability of survival at week 24, 48 and 72 is reported below. | |
| End point type | Secondary |
| End point timeframe: At Week 24, Week 48 and Week 72 | |

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|--|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| Kaplan-Meier estimates (% , 95% CI) - Week 24 | 98.6 (96.4 to 99.5) | 100.0 (100.0 to 100.0) | 93.9 (88.5 to 96.8) | |
| Kaplan-Meier estimates (% , 95% CI) - Week 48 | 93.3 (89.7 to 95.7) | 87.5 (66.1 to 95.8) | 86.1 (79.2 to 90.8) | |
| Kaplan-Meier estimates (% , 95% CI) - Week 72 | 89.7 (85.5 to 92.7) | 87.5 (66.1 to 95.8) | 81.0 (73.5 to 86.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Median time to progression or death with 95% CI [months]

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - Median time to progression or death with 95% CI [months] |
|-----------------|--|

End point description:

Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause.

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

End point timeframe:

Up to approximately 38 months

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (30.9 to 999) | 999 (31.0 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - number of censored participants and number of deaths

| | |
|-----------------|--|
| End point title | Overall Survival (OS) - number of censored participants and number of deaths |
|-----------------|--|

End point description:

Overall survival (OS) defined as the time from date of start of treatment to date of death due to any cause.

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

End point timeframe:

Up to approximately 38 months

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|---|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Participants | | | | |
| No. of censored (no death), n | 240 | 17 | 94 | |
| No. of events (deaths due to any cause), n | 67 | 9 | 60 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) - Kaplan-Meier estimates (% , 95% CI)

| | |
|-----------------|---|
| End point title | Overall response rate (ORR) - Kaplan-Meier estimates (% , 95% CI) |
|-----------------|---|

End point description:

Overall response rate (ORR) is the best overall response (BOR) of complete response (CR) or partial response (PR) as defined by RECIST 1.1.

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

End point timeframe:

At week 24

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|---|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 307 | 26 | 154 | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| ORR by week 24 - (BOR of CR or PR) (confirmed) | 22.8 (18.2 to 27.9) | 23.1 (9.0 to 43.6) | 11.7 (7.1 to 17.8) | |
| ORR by week 24 - (BOR of CR or PR) (unconfirmed) | 24.8 (20.0 to 30.0) | 30.8 (14.3 to 51.8) | 16.2 (10.8 to 23.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30

| | |
|-----------------|---|
| End point title | Change from baseline at week 24 of patient reported Quality of Life (QoL) via EORTC QLQ-C30 |
|-----------------|---|

End point description:

The QLQ-C30 is the core questionnaire of the EORTC QLQ, which has been developed for the assessment of the health-related QOL of cancer patients participating in international clinical trials. Using a linear transformation to standardize the raw scores, all scores finally range from 0 to 100,

where a higher score represents a higher response level, e.g., a higher ("better") level of functioning (applies to the first 6 items, items 1 to 6), but a higher ("worse") level of symptoms (applies to the last 9 items, items 7 to 15). There is no aggregated total score, i.e., all scale scores were analyzed separately.

CfBaW24 = change from baseline at week 24

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Change from Baseline to Week 24 | |

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | ribociclib + letrozole cohort B |
|---|---------------------------------------|--|--|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 307 | 26 | 154 | 180 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Global health status-CfBaW24 (n=181,15,75,90) | 8.8 (± 23.7) | 11.7 (± 20.8) | 5.0 (± 26.2) | 6.1 (± 25.4) |
| Physical Functioning-CfBaW24 (n=183,15,75,90) | -3.1 (± 19.9) | -3.6 (± 10.7) | -2.2 (± 17.7) | -2.4 (± 16.7) |
| Role Functioning-CfBaW24 (n=182,15,75,90) | -6.6 (± 31.9) | -17 (± 21.8) | -1.3 (± 34.7) | -3.9 (± 33.3) |
| Emotional Functioning-CfBaW24 (n=182,15,75,90) | -9.6 (± 24.2) | -9.4 (± 25.0) | -3.6 (± 21.8) | -4.6 (± 22.4) |
| Cognitive Functioning-CfBaW24 (n=182,15,75,90) | 2.7 (± 23.7) | 2.2 (± 28.1) | 1.1 (± 21.6) | 1.3 (± 22.7) |
| Social Functioning-CfBaW24 (n=181,15,75,90) | -6.9 (± 27.9) | -16 (± 21.3) | -5.3 (± 31.3) | -7.0 (± 30.0) |
| Fatigue -CfBaW24 (n=182,15,75,90) | 6.3 (± 25.9) | 11.1 (± 20.6) | 3.9 (± 27.1) | 5.1 (± 26.1) |
| Nausea / Vomiting-CfBaW24 (n=182,15,75,90) | 0.1 (± 16.7) | 1.1 (± 22.2) | -4.9 (± 19.1) | -3.9 (± 19.7) |
| Pain-CfBaW24 (n=182,15,74,89) | 13.2 (± 31.9) | 15.6 (± 24.8) | 9.0 (± 27.6) | 10.1 (± 27.1) |
| Dyspnoea -CfBaW24 (n=182,15,75,90) | 3.8 (± 32.4) | 4.4 (± 21.3) | -5.3 (± 30.5) | -3.7 (± 29.3) |
| Insomnia-CfBaW24 (n=183, 15,75,90) | 4.2 (± 33.2) | 6.7 (± 31.4) | 4.9 (± 32.7) | 5.2 (± 32.3) |
| Appetite loss-CfBaW24 (n=181, 15, 74, 89) | 11.2 (± 33.7) | 6.7 (± 28.7) | 1.4 (± 30.9) | 2.2 (± 30.5) |
| Constipation-CfBaW24 (n=183,15,74,89) | -2.7 (± 26.6) | 2.2 (± 26.6) | -3.6 (± 27.9) | -2.6 (± 27.6) |
| Diarrhea-CfBaW24 (n=182,15,74,89) | 2.6 (± 24.6) | 0.0 (± 45.4) | 2.3 (± 27.2) | 1.9 (± 30.7) |
| Financial Problems-CfBaW24 (n=179,15,73,88) | 0.2 (± 27.7) | -4.4 (± 24.8) | -1.4 (± 25.1) | -1.9 (± 24.9) |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7)

| | |
|-----------------|--|
| End point title | Patient reported Quality of Life (QoL) via EORTC BR-23 - change from baseline at Week 24 (Cycle 7) |
|-----------------|--|

End point description:

To evaluate health related quality of life (QoL) via EORTC BR-23. The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales / single items of the QLQ-C30, i.e., all scores finally range from 0 to 100, where a higher score represents a higher response level, e.g., a higher ("better") level of functioning, (applies to the first 4 items, items 1 to 4) but a higher ("worse") level of symptoms (applies to the last 4 items, items 5 to 8).

CfBaC7 = change from baseline at cycle 7

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

End point timeframe:

Baseline and Week 24 (Cycle 7)

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | ribociclib + letrozole cohort B |
|--|---------------------------------------|--|--|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 307 | 26 | 154 | 180 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| BODY IMAGE-CfBaC7 (n=167,15,72,87) | -1.5 (± 18.2) | -0.6 (± 22.2) | 0.4 (± 22.7) | 0.2 (± 22.5) |
| SEXUAL FUNCTIONING- CfBaC7 (n=120,13,60,73) | -1.1 (± 17.7) | 0.0 (± 24.5) | 0.8 (± 18.0) | 0.7 (± 19.1) |
| SEXUAL ENJOYMENT- CfBaC7 (n=18,2,18,20) | -1.9 (± 31.3) | -17 (± 23.6) | 7.4 (± 26.9) | 5.0 (± 27.1) |
| FUTURE PERSPECTIVE-CfBaC7 (n=172,15,74,89) | -20 (± 33.4) | -24 (± 26.6) | -12 (± 26.2) | -14 (± 26.5) |
| SYSTEMATIC THERAPY-CfBaC7 (n=180,15,74,89) | -9.4 (± 16.6) | -13 (± 22.3) | -6.0 (± 14.9) | -7.1 (± 16.4) |
| BREAST SYMPTOMS- CfBaC7 (n=172,15,73,88) | 3.3 (± 15.7) | 8.3 (± 22.7) | 0.9 (± 17.5) | 2.2 (± 18.6) |
| ARM SYMPTOMS - CfBaC7 (n=175,15,74,89) | 4.1 (± 21.1) | -1.5 (± 22.6) | -2.1 (± 18.1) | -2.0 (± 18.8) |
| HAIR LOSS -CfBaC7 (n=23, 2,14,16) | -22 (± 43.4) | -17 (± 23.6) | -14 (± 33.9) | -15 (± 32.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 10% deterioration in EORTC global health status

| | |
|-----------------|---|
| End point title | Time to 10% deterioration in EORTC global health status |
|-----------------|---|

End point description:

Time to 10% deterioration in the European Organisation for Research and Treatment of Cancer (EORTC) global health status

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

End point timeframe:

up to approximately 10 months

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | Total |
|----------------------------------|---------------------------------------|--|--|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 307 | 26 | 154 | 487 |
| Units: months | | | | |
| median (confidence interval 95%) | 3.3 (2.8 to 4.6) | 3.7 (1.8 to 10.1) | 2.8 (1.8 to 4.6) | 3.0 (2.8 to 4.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

| | |
|--|--|
| End point title | Number of Participants with Treatment Emergent Adverse Events (TEAE) |
| End point description: | |
| Adverse Events (AEs) were separated into TEAEs (defined as AEs occurring/worsening from first study drug treatment until 30 days after the last study drug treatment) and AEs in the pre-/post-treatment period. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 72 | |

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | |
|---|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 319 | 26 | 157 | |
| Units: Number of Participants | | | | |
| Total AEs (i.e., Includes any type of AE.) | 318 | 25 | 157 | |
| Serious AEs | 97 | 5 | 45 | |
| Non-serious AEs | 317 | 25 | 157 | |
| AEs with suspected relationship to ribociclib | 302 | 25 | 144 | |
| AEs leading to discontinuation of ribociclib | 76 | 7 | 38 | |
| AEs with fatal outcome | 6 | 0 | 6 | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

| | |
|-----------------|----------------------|
| End point title | All Collected Deaths |
|-----------------|----------------------|

End point description:

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration of 1150 days (approx 3.15 years). (Treatment duration ranged from 2 days to 1120 days). Deaths post treatment survival follow up were collected after the on- treatment period, up to approx. 3.15 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

on-treatment deaths: up to approx 3.15 years; all deaths: approx 3.15 years

| End point values | ribociclib + letrozole cohort A | ribociclib + letrozole cohort B1 | ribociclib + letrozole cohort B2 | Total |
|----------------------------------|---------------------------------------|--|--|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 319 | 26 | 157 | 502 |
| Units: Participants | | | | |
| on-treatment deaths | 6 | 0 | 6 | 12 |
| Total deaths (n=307,26,154, 487) | 67 | 9 | 60 | 136 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days, up to a maximum duration of 1150 days (approx. 3.15 years). (Treatment duration ranged from 2 days to 1120 days.)

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Cohort B:pr, pe, po Male or Female naïve+pre-tr. |
|-----------------------|--|

Reporting group description:

Cohort B:pr, pe, po Male or Female naïve+pre-tr.

| | |
|-----------------------|----------------------------|
| Reporting group title | Cohort A:po male or Female |
|-----------------------|----------------------------|

Reporting group description:

Cohort A:po male or Female

| | |
|-----------------------|---|
| Reporting group title | Cohort B2:pr, pe, po Male or Female pre-tr. |
|-----------------------|---|

Reporting group description:

Cohort B2:pr, pe, po Male or Female pre-tr.

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| | |
|-----------------------|-------------------------------|
| Reporting group title | Cohort B1:pr, pe Female naïve |
|-----------------------|-------------------------------|

Reporting group description:

Cohort B1:pr, pe Female naïve

| Serious adverse events | Cohort B:pr, pe, po Male or Female naïve+pre-tr. | Cohort A:po male or Female | Cohort B2:pr, pe, po Male or Female pre-tr. |
|---|--|----------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 50 / 183 (27.32%) | 97 / 319 (30.41%) | 45 / 157 (28.66%) |
| number of deaths (all causes) | 6 | 6 | 6 |
| number of deaths resulting from adverse events | 1 | 1 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| BRONCHIAL CARCINOMA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CANCER PAIN | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLON CANCER | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALIGNANT PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| METASTASES TO BONE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| METASTASES TO SPINE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RENAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SQUAMOUS CELL CARCINOMA OF THE TONGUE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 0 / 157 (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 |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| CIRCULATORY COLLAPSE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTENSIVE CRISIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOTENSION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 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 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COMPLICATION OF DEVICE INSERTION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEATH | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 | 2 / 183 (1.09%) | 0 / 319 (0.00%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GENERAL PHYSICAL HEALTH | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| DETERIORATION | | | |
| subjects affected / exposed | 5 / 183 (2.73%) | 2 / 319 (0.63%) | 5 / 157 (3.18%) |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 3 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IMPAIRED HEALING | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 1 / 319 (0.31%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 6 / 319 (1.88%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| PELVIC PAIN | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 | | | |
| ASTHMA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPNOEA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 183 (1.64%) | 9 / 319 (2.82%) | 3 / 157 (1.91%) |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 10 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| DYSпноEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERVENTILATION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 3 / 319 (0.94%) | 3 / 157 (1.91%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| PNEUMONITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 7 / 319 (2.19%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| PULMONARY FIBROSIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY FAILURE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| Psychiatric disorders | | | |
| DEPRESSION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANIC ATTACK | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SOMATIC SYMPTOM DISORDER | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| Product issues | | | |
| DEVICE LOOSENING | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 5 / 319 (1.57%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 3 / 319 (0.94%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BLOOD BILIRUBIN INCREASED | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-REACTIVE PROTEIN INCREASED | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMOGLOBIN DECREASED | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 0 / 157 (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 |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 0 / 157 (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 |
| Injury, poisoning and procedural complications | | | |
| ACCIDENT | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 0 / 157 (0.00%) |
| 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 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FALL | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (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 |
| HIP FRACTURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INCISIONAL HERNIA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| JAW FRACTURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POST-TRAUMATIC PAIN | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POSTOPERATIVE ADHESION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PROCEDURAL COMPLICATION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RIB FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (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 |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 2 / 319 (0.63%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRADYARRHYTHMIA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| Nervous system disorders | | | |
| CEREBRAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| DIZZINESS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| HEADACHE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MONOPLÉGIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| PARAESTHESIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIPHERAL NERVE LESION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 4 / 319 (1.25%) | 4 / 157 (2.55%) |
| occurrences causally related to treatment / all | 10 / 12 | 10 / 11 | 10 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE NEUTROPENIA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 183 (1.64%) | 0 / 319 (0.00%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| HYPERFIBRINOLYSIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LEUKOPENIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 2 / 319 (0.63%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAL HAEMORRHAGE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| DIARRHOEA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 3 / 319 (0.94%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (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 |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ILEUS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| INTESTINAL STRANGULATION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NAUSEA | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 7 / 319 (2.19%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 8 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| VOMITING | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| BILE DUCT STENOSIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BILIARY COLIC | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| DRUG-INDUCED LIVER INJURY | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 5 / 319 (1.57%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 6 / 6 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HEPATIC CIRRHOSIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HEPATOTOXICITY | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| JAUNDICE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 and subcutaneous tissue disorders | | | |
| SKIN ULCER | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 5 / 319 (1.57%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| HAEMATURIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| KIDNEY CONGESTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 DISORDER | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 FAILURE | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RENAL IMPAIRMENT | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URETERIC STENOSIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| URETEROLITHIASIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY INCONTINENCE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 RETENTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 | | | |
| HYPERTHYROIDISM | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| BONE LESION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BONE PAIN | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 2 / 319 (0.63%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FLANK PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LUMBAR SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MOBILITY DECREASED | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 CHEST PAIN | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OSTEITIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OSTEONECROSIS OF JAW | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (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 |
| SPINAL PAIN | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| ABDOMINAL ABSCESS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABSCESS JAW | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| APPENDICITIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ATYPICAL PNEUMONIA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLECYSTITIS INFECTIVE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CYSTITIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CYSTITIS ESCHERICHIA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 0 / 319 (0.00%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EMPHYSEMATOUS CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ERYSIPELAS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ESCHERICHIA INFECTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE INFECTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HELICOBACTER GASTRITIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFECTIOUS PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MASTITIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 8 / 319 (2.51%) | 2 / 157 (1.27%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 8 | 1 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 2 | 1 / 1 |
| PROTEUS INFECTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (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 |
| RESPIRATORY SYNCYTIAL VIRUS INFECTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| 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 | 0 / 183 (0.00%) | 3 / 319 (0.94%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UROSEPSIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 319 (0.63%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEHYDRATION | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 319 (0.31%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOPHAGIA | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 319 (0.31%) | 0 / 157 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TUMOUR LYSIS SYNDROME | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 319 (0.00%) | 1 / 157 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------|-------|------------------|--|
| Serious adverse events | Total | Cohort B1:pr, pe | |
|-------------------------------|-------|------------------|--|

| | | Female naïve | |
|---|--------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 147 / 502 (29.28%) | 5 / 26 (19.23%) | |
| number of deaths (all causes) | 12 | 0 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| BRONCHIAL CARCINOMA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CANCER PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLON CANCER | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MALIGNANT PLEURAL EFFUSION | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METASTASES TO BONE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METASTASES TO SPINE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL CELL CARCINOMA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|----------------|--|
| SQUAMOUS CELL CARCINOMA OF THE TONGUE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| CIRCULATORY COLLAPSE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSIVE CRISIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTENSION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| CHEST PAIN | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COMPLICATION OF DEVICE INSERTION | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEATH | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| FATIGUE | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 7 / 502 (1.39%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IMPAIRED HEALING | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 7 / 502 (1.39%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|------------------|----------------|--|
| PELVIC PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ASTHMA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 12 / 502 (2.39%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 13 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERVENTILATION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 6 / 502 (1.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 8 / 502 (1.59%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| PULMONARY FIBROSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| DEPRESSION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANIC ATTACK | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SOMATIC SYMPTOM DISORDER | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| DEVICE LOOSENING | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 6 / 502 (1.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 4 / 502 (0.80%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD BILIRUBIN INCREASED | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-REACTIVE PROTEIN INCREASED | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMOGLOBIN DECREASED | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| ACCIDENT | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CERVICAL VERTEBRAL FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FALL | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMUR FRACTURE | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HIP FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INCISIONAL HERNIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JAW FRACTURE | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST PROCEDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POST-TRAUMATIC PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POSTOPERATIVE ADHESION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PROCEDURAL COMPLICATION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RIB FRACTURE | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER LIMB FRACTURE | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 4 / 502 (0.80%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRADYARRHYTHMIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| CEREBRAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CEREBROVASCULAR ACCIDENT | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEADACHE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MONOPLÉGIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PERIPHERAL NERVE LESION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 8 / 502 (1.59%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 20 / 23 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| HYPERFIBRINOLYSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 4 / 502 (0.80%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ANAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 4 / 502 (0.80%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ILEUS | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| INTESTINAL STRANGULATION | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 9 / 502 (1.79%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 11 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| BILE DUCT STENOSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BILIARY COLIC | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG-INDUCED LIVER INJURY | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 6 / 502 (1.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATIC CIRRHOSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEPATOTOXICITY | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JAUNDICE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| SKIN ULCER | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 6 / 502 (1.20%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 1 / 6 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| HAEMATURIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| KIDNEY CONGESTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL DISORDER | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL IMPAIRMENT | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URETERIC STENOSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URETEROLITHIASIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY INCONTINENCE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY RETENTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| HYPERTHYROIDISM | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BONE LESION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BONE PAIN | | | |
| subjects affected / exposed | 4 / 502 (0.80%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FLANK PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LUMBAR SPINAL STENOSIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MOBILITY DECREASED | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEONECROSIS OF JAW | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL PAIN | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| ABDOMINAL ABSCESS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ABSCESS JAW | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| APPENDICITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS INFECTIVE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYSTITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CYSTITIS ESCHERICHIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| DIVERTICULITIS | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMPHYSEMATOUS CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ERYSIPELAS | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ESCHERICHIA INFECTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE INFECTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HELICOBACTER GASTRITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTIOUS PLEURAL EFFUSION | | | |

| | | | |
|---|------------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MASTITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 10 / 502 (1.99%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 10 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | |
| PROTEUS INFECTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY SYNCYTIAL VIRUS INFECTION | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 502 (0.60%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UROSEPSIS | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERCALCAEMIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOPHAGIA | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TUMOUR LYSIS SYNDROME | | | |
| subjects affected / exposed | 1 / 502 (0.20%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort B:pr, pe, po Male or Female naïve+pre-tr. | Cohort A:po male or Female | Cohort B2:pr, pe, po Male or Female pre- tr. |
|---|--|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 181 / 183 (98.91%) | 315 / 319 (98.75%) | 156 / 157 (99.36%) |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 30 / 183 (16.39%) | 44 / 319 (13.79%) | 19 / 157 (12.10%) |
| occurrences (all) | 35 | 49 | 22 |
| HYPERTENSION | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | 36 / 319 (11.29%) | 7 / 157 (4.46%) |
| occurrences (all) | 13 | 38 | 9 |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed | 74 / 183 (40.44%) | 123 / 319 (38.56%) | 59 / 157 (37.58%) |
| occurrences (all) | 86 | 151 | 70 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 22 / 183 (12.02%) | 35 / 319 (10.97%) | 17 / 157 (10.83%) |
| occurrences (all) | 31 | 37 | 24 |
| PYREXIA | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 23 / 319 (7.21%) | 10 / 157 (6.37%) |
| occurrences (all) | 19 | 31 | 12 |
| Immune system disorders | | | |
| SEASONAL ALLERGY | | | |
| subjects affected / exposed | 6 / 183 (3.28%) | 4 / 319 (1.25%) | 3 / 157 (1.91%) |
| occurrences (all) | 6 | 4 | 3 |
| Reproductive system and breast | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| disorders | | | |
| VULVOVAGINAL DRYNESS | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 4 / 319 (1.25%) | 0 / 157 (0.00%) |
| occurrences (all) | 3 | 5 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 22 / 183 (12.02%) | 53 / 319 (16.61%) | 16 / 157 (10.19%) |
| occurrences (all) | 26 | 66 | 19 |
| DYSPNOEA | | | |
| subjects affected / exposed | 25 / 183 (13.66%) | 49 / 319 (15.36%) | 21 / 157 (13.38%) |
| occurrences (all) | 26 | 58 | 22 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 7 / 183 (3.83%) | 11 / 319 (3.45%) | 2 / 157 (1.27%) |
| occurrences (all) | 9 | 12 | 2 |
| Psychiatric disorders | | | |
| DEPRESSION | | | |
| subjects affected / exposed | 8 / 183 (4.37%) | 7 / 319 (2.19%) | 6 / 157 (3.82%) |
| occurrences (all) | 8 | 9 | 6 |
| INSOMNIA | | | |
| subjects affected / exposed | 26 / 183 (14.21%) | 31 / 319 (9.72%) | 22 / 157 (14.01%) |
| occurrences (all) | 28 | 34 | 23 |
| SLEEP DISORDER | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | 13 / 319 (4.08%) | 6 / 157 (3.82%) |
| occurrences (all) | 10 | 15 | 6 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 36 / 183 (19.67%) | 75 / 319 (23.51%) | 30 / 157 (19.11%) |
| occurrences (all) | 43 | 93 | 33 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 36 / 183 (19.67%) | 66 / 319 (20.69%) | 31 / 157 (19.75%) |
| occurrences (all) | 44 | 82 | 36 |
| BLOOD BILIRUBIN INCREASED | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 16 / 319 (5.02%) | 1 / 157 (0.64%) |
| occurrences (all) | 1 | 17 | 1 |
| BLOOD CREATININE INCREASED | | | |

| | | | |
|--|-------------------|-------------------|-------------------|
| subjects affected / exposed | 12 / 183 (6.56%) | 27 / 319 (8.46%) | 10 / 157 (6.37%) |
| occurrences (all) | 13 | 38 | 11 |
| BLOOD LACTATE DEHYDROGENASE INCREASED | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 17 / 319 (5.33%) | 2 / 157 (1.27%) |
| occurrences (all) | 4 | 22 | 3 |
| BLOOD THYROID STIMULATING HORMONE INCREASED | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 0 / 319 (0.00%) | 0 / 157 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| ELECTROCARDIOGRAM QT PROLONGED | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 23 / 319 (7.21%) | 13 / 157 (8.28%) |
| occurrences (all) | 19 | 29 | 18 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 18 / 183 (9.84%) | 33 / 319 (10.34%) | 13 / 157 (8.28%) |
| occurrences (all) | 20 | 38 | 15 |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 25 / 183 (13.66%) | 40 / 319 (12.54%) | 23 / 157 (14.65%) |
| occurrences (all) | 75 | 164 | 73 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 9 / 183 (4.92%) | 16 / 319 (5.02%) | 9 / 157 (5.73%) |
| occurrences (all) | 12 | 17 | 12 |
| WEIGHT INCREASED | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 7 / 319 (2.19%) | 2 / 157 (1.27%) |
| occurrences (all) | 5 | 7 | 2 |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 18 / 183 (9.84%) | 27 / 319 (8.46%) | 16 / 157 (10.19%) |
| occurrences (all) | 21 | 56 | 19 |
| Injury, poisoning and procedural complications | | | |
| ARTHROPOD BITE | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 3 / 319 (0.94%) | 1 / 157 (0.64%) |
| occurrences (all) | 3 | 3 | 1 |
| ARTHROPOD STING | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 0 / 319 (0.00%) | 0 / 157 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| | | | |
|--------------------------------------|-------------------|--------------------|-------------------|
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | 26 / 319 (8.15%) | 8 / 157 (5.10%) |
| occurrences (all) | 17 | 30 | 9 |
| DYSGEUSIA | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | 20 / 319 (6.27%) | 7 / 157 (4.46%) |
| occurrences (all) | 12 | 21 | 8 |
| HEADACHE | | | |
| subjects affected / exposed | 36 / 183 (19.67%) | 56 / 319 (17.55%) | 26 / 157 (16.56%) |
| occurrences (all) | 55 | 90 | 35 |
| HYPOAESTHESIA | | | |
| subjects affected / exposed | 5 / 183 (2.73%) | 3 / 319 (0.94%) | 2 / 157 (1.27%) |
| occurrences (all) | 5 | 3 | 2 |
| POLYNEUROPATHY | | | |
| subjects affected / exposed | 5 / 183 (2.73%) | 16 / 319 (5.02%) | 4 / 157 (2.55%) |
| occurrences (all) | 5 | 17 | 4 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 36 / 183 (19.67%) | 46 / 319 (14.42%) | 29 / 157 (18.47%) |
| occurrences (all) | 60 | 60 | 41 |
| LEUKOPENIA | | | |
| subjects affected / exposed | 39 / 183 (21.31%) | 76 / 319 (23.82%) | 31 / 157 (19.75%) |
| occurrences (all) | 108 | 183 | 63 |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 7 / 319 (2.19%) | 0 / 157 (0.00%) |
| occurrences (all) | 13 | 14 | 0 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 88 / 183 (48.09%) | 162 / 319 (50.78%) | 73 / 157 (46.50%) |
| occurrences (all) | 326 | 558 | 231 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 18 / 183 (9.84%) | 26 / 319 (8.15%) | 17 / 157 (10.83%) |
| occurrences (all) | 23 | 46 | 21 |
| Ear and labyrinth disorders | | | |
| VERTIGO | | | |
| subjects affected / exposed | 17 / 183 (9.29%) | 33 / 319 (10.34%) | 13 / 157 (8.28%) |
| occurrences (all) | 17 | 41 | 13 |
| Eye disorders | | | |

| | | | |
|-----------------------------|-------------------|--------------------|-------------------|
| DRY EYE | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | 23 / 319 (7.21%) | 8 / 157 (5.10%) |
| occurrences (all) | 11 | 24 | 9 |
| LACRIMATION INCREASED | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | 34 / 319 (10.66%) | 9 / 157 (5.73%) |
| occurrences (all) | 11 | 38 | 9 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 15 / 319 (4.70%) | 9 / 157 (5.73%) |
| occurrences (all) | 17 | 21 | 10 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 13 / 183 (7.10%) | 33 / 319 (10.34%) | 10 / 157 (6.37%) |
| occurrences (all) | 20 | 42 | 13 |
| CONSTIPATION | | | |
| subjects affected / exposed | 32 / 183 (17.49%) | 62 / 319 (19.44%) | 28 / 157 (17.83%) |
| occurrences (all) | 43 | 71 | 39 |
| DIARRHOEA | | | |
| subjects affected / exposed | 40 / 183 (21.86%) | 85 / 319 (26.65%) | 32 / 157 (20.38%) |
| occurrences (all) | 57 | 133 | 41 |
| DRY MOUTH | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | 28 / 319 (8.78%) | 9 / 157 (5.73%) |
| occurrences (all) | 10 | 30 | 9 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 25 / 319 (7.84%) | 12 / 157 (7.64%) |
| occurrences (all) | 14 | 28 | 12 |
| NAUSEA | | | |
| subjects affected / exposed | 77 / 183 (42.08%) | 130 / 319 (40.75%) | 68 / 157 (43.31%) |
| occurrences (all) | 108 | 202 | 97 |
| STOMATITIS | | | |
| subjects affected / exposed | 27 / 183 (14.75%) | 33 / 319 (10.34%) | 23 / 157 (14.65%) |
| occurrences (all) | 30 | 40 | 26 |
| TOOTHACHE | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 9 / 319 (2.82%) | 2 / 157 (1.27%) |
| occurrences (all) | 4 | 10 | 2 |
| VOMITING | | | |

| | | | |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 31 / 183 (16.94%) 63 | 66 / 319 (20.69%) 93 | 26 / 157 (16.56%) 53 |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 57 / 183 (31.15%) | 119 / 319 (37.30%) | 52 / 157 (33.12%) |
| occurrences (all) | 63 | 127 | 56 |
| DRY SKIN | | | |
| subjects affected / exposed | 15 / 183 (8.20%) | 24 / 319 (7.52%) | 12 / 157 (7.64%) |
| occurrences (all) | 16 | 27 | 13 |
| ERYTHEMA | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | 9 / 319 (2.82%) | 9 / 157 (5.73%) |
| occurrences (all) | 10 | 9 | 9 |
| PRURITUS | | | |
| subjects affected / exposed | 18 / 183 (9.84%) | 45 / 319 (14.11%) | 15 / 157 (9.55%) |
| occurrences (all) | 19 | 53 | 15 |
| RASH | | | |
| subjects affected / exposed | 19 / 183 (10.38%) | 47 / 319 (14.73%) | 17 / 157 (10.83%) |
| occurrences (all) | 25 | 60 | 22 |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 39 / 183 (21.31%) | 57 / 319 (17.87%) | 30 / 157 (19.11%) |
| occurrences (all) | 47 | 76 | 35 |
| BACK PAIN | | | |
| subjects affected / exposed | 24 / 183 (13.11%) | 37 / 319 (11.60%) | 20 / 157 (12.74%) |
| occurrences (all) | 29 | 42 | 23 |
| BONE PAIN | | | |
| subjects affected / exposed | 15 / 183 (8.20%) | 35 / 319 (10.97%) | 9 / 157 (5.73%) |
| occurrences (all) | 18 | 42 | 9 |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 6 / 183 (3.28%) | 12 / 319 (3.76%) | 4 / 157 (2.55%) |
| occurrences (all) | 7 | 13 | 5 |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 21 / 319 (6.58%) | 12 / 157 (7.64%) |
| occurrences (all) | 15 | 27 | 12 |
| MYALGIA | | | |

| | | | |
|---|--------------------|----------------------------------|-------------------|
| subjects affected / exposed | 6 / 183 (3.28%) | 18 / 319 (5.64%) | 6 / 157 (3.82%) |
| occurrences (all) | 7 | 18 | 7 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 23 / 183 (12.57%) | 52 / 319 (16.30%) | 20 / 157 (12.74%) |
| occurrences (all) | 35 | 68 | 30 |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 5 / 183 (2.73%) | 19 / 319 (5.96%) | 4 / 157 (2.55%) |
| occurrences (all) | 6 | 25 | 5 |
| CYSTITIS | | | |
| subjects affected / exposed | 9 / 183 (4.92%) | 21 / 319 (6.58%) | 6 / 157 (3.82%) |
| occurrences (all) | 10 | 25 | 7 |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 2 / 319 (0.63%) | 1 / 157 (0.64%) |
| occurrences (all) | 3 | 2 | 1 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 49 / 183 (26.78%) | 94 / 319 (29.47%) | 39 / 157 (24.84%) |
| occurrences (all) | 74 | 131 | 56 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 17 / 183 (9.29%) | 31 / 319 (9.72%) | 16 / 157 (10.19%) |
| occurrences (all) | 23 | 45 | 21 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 19 / 183 (10.38%) | 44 / 319 (13.79%) | 18 / 157 (11.46%) |
| occurrences (all) | 20 | 45 | 19 |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 6 / 319 (1.88%) | 2 / 157 (1.27%) |
| occurrences (all) | 6 | 18 | 2 |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 5 / 183 (2.73%) | 8 / 319 (2.51%) | 3 / 157 (1.91%) |
| occurrences (all) | 5 | 10 | 3 |
| Non-serious adverse events | Total | Cohort B1:pr, pe Female naïve | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 496 / 502 (98.80%) | 25 / 26 (96.15%) | |
| Vascular disorders | | | |

| | | | |
|--|--------------------|------------------|--|
| HOT FLUSH | | | |
| subjects affected / exposed | 74 / 502 (14.74%) | 11 / 26 (42.31%) | |
| occurrences (all) | 84 | 13 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 47 / 502 (9.36%) | 4 / 26 (15.38%) | |
| occurrences (all) | 51 | 4 | |
| General disorders and administration site conditions | | | |
| FATIGUE | | | |
| subjects affected / exposed | 197 / 502 (39.24%) | 15 / 26 (57.69%) | |
| occurrences (all) | 237 | 16 | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 57 / 502 (11.35%) | 5 / 26 (19.23%) | |
| occurrences (all) | 68 | 7 | |
| PYREXIA | | | |
| subjects affected / exposed | 37 / 502 (7.37%) | 4 / 26 (15.38%) | |
| occurrences (all) | 50 | 7 | |
| Immune system disorders | | | |
| SEASONAL ALLERGY | | | |
| subjects affected / exposed | 10 / 502 (1.99%) | 3 / 26 (11.54%) | |
| occurrences (all) | 10 | 3 | |
| Reproductive system and breast disorders | | | |
| VULVOVAGINAL DRYNESS | | | |
| subjects affected / exposed | 7 / 502 (1.39%) | 3 / 26 (11.54%) | |
| occurrences (all) | 8 | 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 75 / 502 (14.94%) | 6 / 26 (23.08%) | |
| occurrences (all) | 92 | 7 | |
| DYSPNOEA | | | |
| subjects affected / exposed | 74 / 502 (14.74%) | 4 / 26 (15.38%) | |
| occurrences (all) | 84 | 4 | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 18 / 502 (3.59%) | 5 / 26 (19.23%) | |
| occurrences (all) | 21 | 7 | |
| Psychiatric disorders | | | |

| | | | |
|---|--------------------|-----------------|--|
| DEPRESSION | | | |
| subjects affected / exposed | 15 / 502 (2.99%) | 2 / 26 (7.69%) | |
| occurrences (all) | 17 | 2 | |
| INSOMNIA | | | |
| subjects affected / exposed | 57 / 502 (11.35%) | 4 / 26 (15.38%) | |
| occurrences (all) | 62 | 5 | |
| SLEEP DISORDER | | | |
| subjects affected / exposed | 23 / 502 (4.58%) | 4 / 26 (15.38%) | |
| occurrences (all) | 25 | 4 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 111 / 502 (22.11%) | 6 / 26 (23.08%) | |
| occurrences (all) | 136 | 10 | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 102 / 502 (20.32%) | 5 / 26 (19.23%) | |
| occurrences (all) | 126 | 8 | |
| BLOOD BILIRUBIN INCREASED | | | |
| subjects affected / exposed | 17 / 502 (3.39%) | 0 / 26 (0.00%) | |
| occurrences (all) | 18 | 0 | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 39 / 502 (7.77%) | 2 / 26 (7.69%) | |
| occurrences (all) | 51 | 2 | |
| BLOOD LACTATE DEHYDROGENASE INCREASED | | | |
| subjects affected / exposed | 20 / 502 (3.98%) | 1 / 26 (3.85%) | |
| occurrences (all) | 26 | 1 | |
| BLOOD THYROID STIMULATING HORMONE INCREASED | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 2 / 26 (7.69%) | |
| occurrences (all) | 2 | 2 | |
| ELECTROCARDIOGRAM QT PROLONGED | | | |
| subjects affected / exposed | 37 / 502 (7.37%) | 1 / 26 (3.85%) | |
| occurrences (all) | 48 | 1 | |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |

| | | | |
|--|-------------------|------------------|--|
| subjects affected / exposed | 51 / 502 (10.16%) | 5 / 26 (19.23%) | |
| occurrences (all) | 58 | 5 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 65 / 502 (12.95%) | 2 / 26 (7.69%) | |
| occurrences (all) | 239 | 2 | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 25 / 502 (4.98%) | 0 / 26 (0.00%) | |
| occurrences (all) | 29 | 0 | |
| WEIGHT INCREASED | | | |
| subjects affected / exposed | 11 / 502 (2.19%) | 2 / 26 (7.69%) | |
| occurrences (all) | 12 | 3 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 45 / 502 (8.96%) | 2 / 26 (7.69%) | |
| occurrences (all) | 77 | 2 | |
| Injury, poisoning and procedural complications | | | |
| ARTHROPOD BITE | | | |
| subjects affected / exposed | 6 / 502 (1.20%) | 2 / 26 (7.69%) | |
| occurrences (all) | 6 | 2 | |
| ARTHROPOD STING | | | |
| subjects affected / exposed | 2 / 502 (0.40%) | 2 / 26 (7.69%) | |
| occurrences (all) | 2 | 2 | |
| Nervous system disorders | | | |
| DIZZINESS | | | |
| subjects affected / exposed | 38 / 502 (7.57%) | 4 / 26 (15.38%) | |
| occurrences (all) | 47 | 8 | |
| DYSGEUSIA | | | |
| subjects affected / exposed | 31 / 502 (6.18%) | 4 / 26 (15.38%) | |
| occurrences (all) | 33 | 4 | |
| HEADACHE | | | |
| subjects affected / exposed | 92 / 502 (18.33%) | 10 / 26 (38.46%) | |
| occurrences (all) | 145 | 20 | |
| HYPOAESTHESIA | | | |
| subjects affected / exposed | 8 / 502 (1.59%) | 3 / 26 (11.54%) | |
| occurrences (all) | 8 | 3 | |
| POLYNEUROPATHY | | | |

| | | | |
|---|---------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 21 / 502 (4.18%) 22 | 1 / 26 (3.85%) 1 | |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 82 / 502 (16.33%) 120 | 7 / 26 (26.92%) 19 | |
| LEUKOPENIA subjects affected / exposed occurrences (all) | 115 / 502 (22.91%) 291 | 8 / 26 (30.77%) 45 | |
| LYMPHOPENIA subjects affected / exposed occurrences (all) | 9 / 502 (1.79%) 27 | 2 / 26 (7.69%) 13 | |
| NEUTROPENIA subjects affected / exposed occurrences (all) | 250 / 502 (49.80%) 884 | 15 / 26 (57.69%) 95 | |
| THROMBOCYTOPENIA subjects affected / exposed occurrences (all) | 44 / 502 (8.76%) 69 | 1 / 26 (3.85%) 2 | |
| Ear and labyrinth disorders VERTIGO subjects affected / exposed occurrences (all) | 50 / 502 (9.96%) 58 | 4 / 26 (15.38%) 4 | |
| Eye disorders DRY EYE subjects affected / exposed occurrences (all) | 33 / 502 (6.57%) 35 | 2 / 26 (7.69%) 2 | |
| LACRIMATION INCREASED subjects affected / exposed occurrences (all) | 45 / 502 (8.96%) 49 | 2 / 26 (7.69%) 2 | |
| Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all) | 29 / 502 (5.78%) 38 | 5 / 26 (19.23%) 7 | |
| ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all) | 46 / 502 (9.16%) 62 | 3 / 26 (11.54%) 7 | |
| CONSTIPATION | | | |

| | | | |
|--|--------------------|-----------------|--|
| subjects affected / exposed | 94 / 502 (18.73%) | 4 / 26 (15.38%) | |
| occurrences (all) | 114 | 4 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 125 / 502 (24.90%) | 8 / 26 (30.77%) | |
| occurrences (all) | 190 | 16 | |
| DRY MOUTH | | | |
| subjects affected / exposed | 38 / 502 (7.57%) | 1 / 26 (3.85%) | |
| occurrences (all) | 40 | 1 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 39 / 502 (7.77%) | 2 / 26 (7.69%) | |
| occurrences (all) | 42 | 2 | |
| NAUSEA | | | |
| subjects affected / exposed | 207 / 502 (41.24%) | 9 / 26 (34.62%) | |
| occurrences (all) | 310 | 11 | |
| STOMATITIS | | | |
| subjects affected / exposed | 60 / 502 (11.95%) | 4 / 26 (15.38%) | |
| occurrences (all) | 70 | 4 | |
| TOOTHACHE | | | |
| subjects affected / exposed | 13 / 502 (2.59%) | 2 / 26 (7.69%) | |
| occurrences (all) | 14 | 2 | |
| VOMITING | | | |
| subjects affected / exposed | 97 / 502 (19.32%) | 5 / 26 (19.23%) | |
| occurrences (all) | 156 | 10 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 176 / 502 (35.06%) | 5 / 26 (19.23%) | |
| occurrences (all) | 190 | 7 | |
| DRY SKIN | | | |
| subjects affected / exposed | 39 / 502 (7.77%) | 3 / 26 (11.54%) | |
| occurrences (all) | 43 | 3 | |
| ERYTHEMA | | | |
| subjects affected / exposed | 19 / 502 (3.78%) | 1 / 26 (3.85%) | |
| occurrences (all) | 19 | 1 | |
| PRURITUS | | | |
| subjects affected / exposed | 63 / 502 (12.55%) | 3 / 26 (11.54%) | |
| occurrences (all) | 72 | 4 | |

| | | | |
|---|-------------------|-----------------|--|
| RASH | | | |
| subjects affected / exposed | 66 / 502 (13.15%) | 2 / 26 (7.69%) | |
| occurrences (all) | 85 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 96 / 502 (19.12%) | 9 / 26 (34.62%) | |
| occurrences (all) | 123 | 12 | |
| BACK PAIN | | | |
| subjects affected / exposed | 61 / 502 (12.15%) | 4 / 26 (15.38%) | |
| occurrences (all) | 71 | 6 | |
| BONE PAIN | | | |
| subjects affected / exposed | 50 / 502 (9.96%) | 6 / 26 (23.08%) | |
| occurrences (all) | 60 | 9 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 18 / 502 (3.59%) | 2 / 26 (7.69%) | |
| occurrences (all) | 20 | 2 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 35 / 502 (6.97%) | 2 / 26 (7.69%) | |
| occurrences (all) | 42 | 3 | |
| MYALGIA | | | |
| subjects affected / exposed | 24 / 502 (4.78%) | 0 / 26 (0.00%) | |
| occurrences (all) | 25 | 0 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 75 / 502 (14.94%) | 3 / 26 (11.54%) | |
| occurrences (all) | 103 | 5 | |
| Infections and infestations | | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 24 / 502 (4.78%) | 1 / 26 (3.85%) | |
| occurrences (all) | 31 | 1 | |
| CYSTITIS | | | |
| subjects affected / exposed | 30 / 502 (5.98%) | 3 / 26 (11.54%) | |
| occurrences (all) | 35 | 3 | |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 5 / 502 (1.00%) | 2 / 26 (7.69%) | |
| occurrences (all) | 5 | 2 | |
| NASOPHARYNGITIS | | | |

| | | | |
|------------------------------------|--------------------|------------------|--|
| subjects affected / exposed | 143 / 502 (28.49%) | 10 / 26 (38.46%) | |
| occurrences (all) | 205 | 18 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 48 / 502 (9.56%) | 1 / 26 (3.85%) | |
| occurrences (all) | 68 | 2 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 63 / 502 (12.55%) | 1 / 26 (3.85%) | |
| occurrences (all) | 65 | 1 | |
| HYPERKALAEMIA | | | |
| subjects affected / exposed | 10 / 502 (1.99%) | 2 / 26 (7.69%) | |
| occurrences (all) | 24 | 4 | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 13 / 502 (2.59%) | 2 / 26 (7.69%) | |
| occurrences (all) | 15 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 30 September 2016 | The purpose of this amendment was to include feedback received from BfArM and ECs during the assessment of the initial application. |
| 03 May 2017 | This amendment was intended to update the existing information about ribociclib, to clarify specific aspects of the original protocol and to introduce the option for treatment beyond radiologic progression at the investigators discretion. |
| 14 August 2017 | This amendment was intended to correct mistakes in the protocol |
| 05 May 2019 | This amendment was intended to update the existing information about ribociclib, to clarify specific aspects of the original protocol and to introduce the option for treatment beyond radiologic progression at the investigators discretion. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported