



Clinical trial results:

A Phase III multi-center, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)

Summary

| | |
|--------------------------|--|
| EudraCT number | 2007-000208-34 |
| Trial protocol | SE CZ BE IT ES SK AT FR NL FI DK DE PT HU GB |
| Global end of trial date | 21 August 2019 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2020 |
| First version publication date | 02 September 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CAMN107A2303 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00471497 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, 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 | 21 August 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy (major molecular response (MMR) rate at 12 months) of nilotinib at 400 mg bid with that of imatinib 400 mg qd in newly diagnosed, previously untreated Ph+ CML-CP patients.
- To compare the efficacy (MMR rate at 12 months) of nilotinib at 300 mg bid with that of imatinib 400 mg qd in newly diagnosed, previously untreated Ph+ CML-CP patients.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.clinicaltrials.gov/ct2/show/study?term=2007-000208-34&rank=1> for complete trial results.

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 | 31 July 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Brazil: 67 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Colombia: 3 |
| Country: Number of subjects enrolled | Czech Republic: 5 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | Egypt: 8 |
| Country: Number of subjects enrolled | Finland: 11 |
| Country: Number of subjects enrolled | France: 86 |
| Country: Number of subjects enrolled | Germany: 51 |

| | |
|--------------------------------------|--------------------------------------|
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | Hungary: 1 |
| Country: Number of subjects enrolled | Italy: 63 |
| Country: Number of subjects enrolled | Japan: 77 |
| Country: Number of subjects enrolled | Korea, Republic of: 58 |
| Country: Number of subjects enrolled | Malaysia: 1 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Norway: 10 |
| Country: Number of subjects enrolled | Poland: 42 |
| Country: Number of subjects enrolled | Russian Federation: 13 |
| Country: Number of subjects enrolled | Singapore: 18 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Country: Number of subjects enrolled | South Africa: 14 |
| Country: Number of subjects enrolled | Spain: 40 |
| Country: Number of subjects enrolled | Sweden: 27 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | Taiwan: 11 |
| Country: Number of subjects enrolled | Thailand: 39 |
| Country: Number of subjects enrolled | Turkey: 13 |
| Country: Number of subjects enrolled | United States: 94 |
| Country: Number of subjects enrolled | Venezuela, Bolivarian Republic of: 7 |
| Worldwide total number of subjects | 846 |
| EEA total number of subjects | 397 |

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) | 748 |
| From 65 to 84 years | 97 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The study over-enrolled, and 846 patients (283 in the imatinib 400 mg arm, 282 in the nilotinib 300 mg arm and 281 in the nilotinib 400 mg arm) were randomized. DP = disease progression, SOR/TF = Suboptimal response or treatment failure

Pre-assignment

Screening details:

Randomization was planned for a total of 771 patients.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Core Treatment Phase |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Imatinib 400 mg QD |

Arm description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Imatinib |
| Investigational medicinal product code | STI571 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Imatinib was supplied as 100 mg and/or 400 mg tablets. Patients imatinib 400 mg qd orally. If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg bid orally. Imatinib was to be taken with food and a large glass of water.

| | |
|------------------|----------------------|
| Arm title | Nilotinib 300 mg BID |
|------------------|----------------------|

Arm description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nilotinib |
| Investigational medicinal product code | AMN107 |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 300 mg bid by mouth each morning and evening approximately 12 hours apart.

| | |
|------------------|----------------------|
| Arm title | Nilotinib 400 mg BID |
|------------------|----------------------|

Arm description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nilotinib |
| Investigational medicinal product code | AMN107 |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 400 mg bid by mouth each morning and evening approximately 12 hours apart.

| Number of subjects in period 1 | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID |
|--|--------------------|---------------------|----------------------|
| Started | 283 | 282 | 281 |
| Safety Analysis Set | 280 | 279 | 277 |
| Discon. Core/Did not enter Ext. | 235 | 256 | 278 |
| Discontinued Core/Entered Ext. | 48 ^[1] | 26 ^[2] | 3 ^[3] |
| Completed | 99 | 107 | 99 |
| Not completed | 184 | 175 | 182 |
| Adverse event, serious fatal | 3 | 9 | 3 |
| Sub optimal response or treat. failure | 19 | 11 | 13 |
| Abnormal Test Procedures | 1 | - | 1 |
| Abnormal Laboratory Values | 3 | 9 | 9 |
| Administrative problems | 14 | 14 | 12 |
| Disc. Core/Entered Ext.- SOR/TF | 46 | 26 | 3 |
| Disease Progression | 10 | 2 | 4 |
| Consent withdrawn by subject | 31 | 29 | 34 |
| Disc. Core/Entered Ext. - DP progression | 2 | - | - |
| Adverse event, non-fatal | 43 | 53 | 89 |

| | | | |
|---|---|----|----|
| Condition no longer requires study drug | - | 1 | - |
| Lost to follow-up | 6 | 6 | 3 |
| Protocol deviation | 6 | 15 | 11 |

Notes:

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

Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

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

Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

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

Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Extension Phase |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Imatinib 400 mg QD (Treatment taken during core phase) |

Arm description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Imatinib |
| Investigational medicinal product code | STI571 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Imatinib was supplied as 100 mg and/or 400 mg tablets. Patients imatinib 400 mg qd orally. If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg bid orally. Imatinib was to be taken with food and a large glass of water.

| | |
|------------------|--|
| Arm title | Nilotinib 300 mg BID (Treatment taken during core phase) |
|------------------|--|

Arm description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited

doses were not to be repeated.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nilotinib |
| Investigational medicinal product code | AMN107 |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 300 mg bid by mouth each morning and evening approximately 12 hours apart.

| | |
|------------------|--|
| Arm title | Nilotinib 400 mg BID (Treatment taken during core phase) |
|------------------|--|

Arm description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Nilotinib |
| Investigational medicinal product code | AMN107 |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Nilotinib was supplied as 50 mg, 150 mg, or 200 mg hard gelatin capsules and was dosed on a flat scale and not dosed by body weight. Patients were randomized to receive nilotinib 400 mg bid by mouth each morning and evening approximately 12 hours apart.

| Number of subjects in period 2^[4] | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) |
|---|---|---|---|
| Started | 48 | 26 | 3 |
| Completed | 21 | 12 | 2 |
| Not completed | 27 | 14 | 1 |
| Adverse event, serious fatal | 1 | - | - |
| Consent withdrawn by subject | 3 | 1 | - |
| Adverse event, non-fatal | 9 | 5 | 1 |
| Unsatisfactory therapeutic effect | 8 | 6 | - |
| Lost to follow-up | 2 | - | - |
| Disease Progression | 2 | - | - |
| Protocol deviation | 2 | 2 | - |

Notes:

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

Justification: Extension period was optional a and so not all who completed Core moved into Extension period.

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Imatinib 400 mg QD |
| Reporting group description: | |
| Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated | |
| Reporting group title | Nilotinib 300 mg BID |
| Reporting group description: | |
| Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated. | |
| Reporting group title | Nilotinib 400 mg BID |
| Reporting group description: | |
| Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated. | |

| Reporting group values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID |
|----------------------------|--------------------|---------------------|----------------------|
| Number of subjects | 283 | 282 | 281 |
| Age Categorical | | | |
| Units: Participants | | | |
| <35 years | 63 | 67 | 65 |
| >= 35 - <45 years | 67 | 50 | 59 |
| >=45 - <55 years | 63 | 72 | 65 |
| >=55 - < 65 years | 55 | 57 | 65 |
| >=65 years | 35 | 36 | 27 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 47.1 | 47.2 | 46.7 |
| standard deviation | ± 14.34 | ± 14.53 | ± 13.90 |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 125 | 124 | 106 |
| Male | 158 | 158 | 175 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | 187 | 170 | 185 |

| | | | |
|-----------------|----|----|----|
| Black | 7 | 12 | 11 |
| Asian | 71 | 76 | 66 |
| Native American | 1 | 0 | 2 |
| Other | 17 | 24 | 17 |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 846 | | |
| Age Categorical Units: Participants | | | |
| <35 years | 195 | | |
| >= 35 - <45 years | 176 | | |
| >=45 - <55 years | 200 | | |
| >=55 - < 65 years | 177 | | |
| >=65 years | 98 | | |
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: | | | |
| Female | 355 | | |
| Male | 491 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 542 | | |
| Black | 30 | | |
| Asian | 213 | | |
| Native American | 3 | | |
| Other | 58 | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Imatinib 400 mg QD |
| Reporting group description: Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated | |
| Reporting group title | Nilotinib 300 mg BID |
| Reporting group description: Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated. | |
| Reporting group title | Nilotinib 400 mg BID |
| Reporting group description: Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated. | |
| Reporting group title | Imatinib 400 mg QD (Treatment taken during core phase) |
| Reporting group description: Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated | |
| Reporting group title | Nilotinib 300 mg BID (Treatment taken during core phase) |
| Reporting group description: Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated. | |
| Reporting group title | Nilotinib 400 mg BID (Treatment taken during core phase) |
| Reporting group description: Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules | |

whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

Primary: Major molecular response rate (MMR) at 12 months between all 3 arms - with imputation

| | |
|-----------------|---|
| End point title | Major molecular response rate (MMR) at 12 months between all 3 arms - with imputation |
|-----------------|---|

End point description:

MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

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

End point timeframe:

Baseline, 12 months

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 22.3 (17.6 to 27.6) | 44.3 (38.4 to 50.3) | 42.7 (36.8 to 48.7) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Imatinib 400 mg qd vs nilotinib 300mg bid |
| Comparison groups | Imatinib 400 mg QD v Nilotinb 300 mg BID |
| Number of subjects included in analysis | 565 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in response rate |
| Point estimate | 22.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.5 |
| upper limit | 29.6 |

| | |
|----------------------------|---|
| Statistical analysis title | Imatinib 400 mg qd vs nilotinib 400mg bid |
| Comparison groups | Imatinib 400 mg QD v Nilotinib 400 mg BID |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 564 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in response rate |
| Point estimate | 20.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.9 |
| upper limit | 28 |

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Low Sokal risk group)

| | |
|------------------------|---|
| End point title | MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Low Sokal risk group) |
| End point description: | MMR is defined as the proportion of patients in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months. |
| End point type | Primary |
| End point timeframe: | 12 months |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|--|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 104 | 103 | 103 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Sokal risk group = Low (n=104,103,103) | 26.0 (17.9 to 35.5) | 40.8 (31.2 to 50.9) | 53.4 (43.3 to 63.3) | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | SS Low: Imatinib 400mg qd vs nilotinib 300mg bid |
| Statistical analysis description: | (Low) |
| Comparison groups | Imatinib 400 mg QD v Nilotinb 300 mg BID |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 14.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.1 |
| upper limit | 27.5 |

| | |
|--|---|
| Statistical analysis title | SS Low: Imatinib 400 mg qd vs nilotinib 400mg bid |
| Statistical analysis description: (Low) | |
| Comparison groups | Imatinib 400 mg QD v Nilotinib 400 mg BID |
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 27.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.6 |
| upper limit | 40.2 |

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Intermediate Sokal risk group)

| | |
|--|---|
| End point title | MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (Intermediate Sokal risk group) |
| End point description: MMR is defined as the proportion of patients in MMR reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months. | |
| End point type | Primary |
| End point timeframe: 12 months | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|---------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 101 | 101 | 100 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 22.8 (15.0 to 32.2) | 50.5 (40.4 to 60.6) | 40.0 (30.3 to 50.3) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | MMR Inter:Imatinib 400mg qd vs nilotinib |
| Statistical analysis description: (Intermediate) | |
| Comparison groups | Imatinib 400 mg QD v Nilotinb 300 mg BID |
| Number of subjects included in analysis | 202 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 27.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15 |
| upper limit | 40.4 |

| | |
|---|---|
| Statistical analysis title | MMR Inter:Imatinib 400mg qd vs nilotinib |
| Statistical analysis description: (Intermediate) | |
| Comparison groups | Imatinib 400 mg QD v Nilotinib 400 mg BID |
| Number of subjects included in analysis | 201 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 17.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.6 |
| upper limit | 29.8 |

Primary: MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (High Sokal risk group)

| | |
|-----------------|---|
| End point title | MMR rates at 12 months between all 3 arms by Sokal risk group with imputation (High Sokal risk group) |
|-----------------|---|

End point description:

MMR is defined as the proportion of patients in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| 12 months | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 78 | 78 | 78 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 16.7 (9.2 to 26.8) | 41.0 (30.0 to 52.7) | 32.1 (21.9 to 43.6) | |

Statistical analyses

| Statistical analysis title | MMR High:Imatinib 400mg qd vs nilotinib |
|---|--|
| Statistical analysis description: | |
| (High) | |
| Comparison groups | Imatinib 400 mg QD v Nilotinb 300 mg BID |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 24.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.7 |
| upper limit | 38.1 |

| Statistical analysis title | MMR High:Imatinib 400mg qd vs nilotinib |
|---|---|
| Statistical analysis description: | |
| (High) | |
| Comparison groups | Imatinib 400 mg QD v Nilotinib 400 mg BID |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 15.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.1 |
| upper limit | 28.6 |

Secondary: Rates of durable MMR at 24 months between all 3 arms

| | |
|---|--|
| End point title | Rates of durable MMR at 24 months between all 3 arms |
| End point description: Durable MMR at 24 months is defined as having MMR both at 12 months and at 24 months, and with no documented loss of MMR between these 12 month and 24 month time points. | |
| End point type | Secondary |
| End point timeframe: 24 months | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 20.5 (15.9 to 25.7) | 41.8 (36.0 to 47.8) | 39.1 (33.4 to 45.1) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Dur. MMR: Imatinib 400mg qd vs nilotinib 300mg bid |
| Comparison groups | Imatinib 400 mg QD v Nilotinb 300 mg BID |
| Number of subjects included in analysis | 565 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 21.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.9 |
| upper limit | 28.8 |

| | |
|---|--|
| Statistical analysis title | Dur. MMR: Imatinib 400mg qd vs nilotinib 400mg bid |
| Comparison groups | Imatinib 400 mg QD v Nilotinib 400 mg BID |
| Number of subjects included in analysis | 564 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in response rate |
| Point estimate | 18.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.3 |
| upper limit | 26 |

Secondary: Rate of complete cytogenetic response (CCyR) in nilotinib treatment arms with imatinib at 12 months and beyond 12 months

| | |
|---|--|
| End point title | Rate of complete cytogenetic response (CCyR) in nilotinib treatment arms with imatinib at 12 months and beyond 12 months |
| End point description: CCyR is defined as 0% Ph+ metaphases based on at least 20 metaphases from bone marrow cytogenetics. Patients with no CCyR as the best response by any specific time point, all missing cytogenetic evaluations by that time point or Ph- at baseline are combined as "Nocomplete cytogenetic response". | |
| End point type | Secondary |
| End point timeframe: 12, 24, 36, 48, 60, 72 months (M) | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| CCyR at M12 | 55.5 | 70.2 | 68.7 | |
| CCyR at M24 | 61.5 | 66.0 | 66.2 | |
| CCyR at M36 | 14.1 | 9.2 | 12.8 | |
| CCyR at M48 | 11.3 | 8.9 | 13.5 | |
| CCyR at M60 | 2.5 | 2.8 | 2.8 | |
| CCyR at M72 | 1.8 | 1.8 | 2.8 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Major molecular response (MMR) at 12 months between two nilotinib arms

| | |
|---|---|
| End point title | Rate of Major molecular response (MMR) at 12 months between two nilotinib arms ^[1] |
| End point description: MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 12 months. | |
| End point type | Secondary |

End point timeframe:

12 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no plan to report statistical analysis for this endpoint

| End point values | Nilotinib 300 mg BID | Nilotinib 400 mg BID | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 282 | 281 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 44.3 (38.4 to 50.3) | 42.7 (36.8 to 48.7) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | MMR: nilotinib 300mg bid vs nilotinib 400mg bid |
| Comparison groups | Nilotinib 300 mg BID v Nilotinib 400 mg BID |
| Number of subjects included in analysis | 563 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6987 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Absolute difference |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.8 |
| upper limit | 6.6 |

Secondary: Rate of MMR at 6 months and beyond 12 months in all 3 treatment arms

| | |
|---|--|
| End point title | Rate of MMR at 6 months and beyond 12 months in all 3 treatment arms |
| End point description: | |
| MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR)) at 6 months and 12 months and beyond 12 months. | |
| End point type | Secondary |
| End point timeframe: | |
| 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|-----------------------------------|---------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| MMR at M6 | 12.0 (8.5 to 16.4) | 33.0 (27.5 to 38.8) | 29.5 (24.3 to 35.2) | |
| MMR at M12 | 22.3 (17.6 to 27.6) | 44.7 (38.8 to 50.7) | 43.1 (37.2 to 49.1) | |
| MMR at M24 | 37.5 (31.8 to 43.4) | 61.7 (55.8 to 67.4) | 59.1 (53.1 to 64.9) | |
| MMR at M36 | 38.5 (32.8 to 44.5) | 59.2 (53.2 to 65.0) | 57.3 (51.3 to 63.2) | |
| MMR at M48 | 43.8 (38.0 to 49.8) | 59.9 (54.0 to 65.7) | 55.2 (49.1 to 61.1) | |
| MMR at M60 | 49.1 (43.2 to 55.1) | 62.8 (56.8 to 68.4) | 61.2 (55.2 to 66.9) | |
| MMR at M72 | 41.7 (35.9 to 47.7) | 52.5 (46.5 to 58.4) | 57.7 (51.6 to 63.5) | |
| MMR at M84 | 40.3 (34.5 to 46.3) | 50.0 (44.0 to 56.0) | 50.9 (44.9 to 56.9) | |
| MMR at M96 | 37.5 (31.8 to 43.4) | 46.1 (40.2 to 52.1) | 46.3 (40.3 to 52.3) | |
| MMR at M108 | 37.5 (31.8 to 43.4) | 43.3 (37.4 to 49.3) | 40.2 (34.4 to 46.2) | |
| MMR at M120 | 36.4 (30.8 to 42.3) | 37.9 (32.3 to 43.9) | 39.1 (33.4 to 45.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

| | |
|---|---|
| End point title | Rate of a ≥ 4 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib |
| End point description: | |
| Molecular response of $\leq 0.01\%$ is defined as BCR-ABL ratio (%) on IS $\leq 0.01\%$ (corresponds to ≥ 4 log reduction of BCR-ABL transcripts from standardized baseline value) | |
| End point type | Secondary |
| End point timeframe: | |
| at 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|---|--------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Molecular response of $\leq 0.01\%$ at 6 months | 1.1 (0.2 to 3.1) | 8.9 (5.8 to 12.8) | 5.7 (3.3 to 9.1) | |

| | | | | |
|---|---------------------|---------------------|---------------------|--|
| Molecular response of $\leq 0.01\%$ at 12 months | 3.9 (2.0 to 6.8) | 12.1 (8.5 to 16.4) | 8.9 (5.8 to 12.9) | |
| Molecular response of $\leq 0.01\%$ at 24 months | 10.2 (7.0 to 14.4) | 24.5 (19.6 to 29.9) | 22.1 (17.4 to 27.4) | |
| Molecular response of $\leq 0.01\%$ at 36 months | 14.1 (10.3 to 18.7) | 29.4 (24.2 to 35.1) | 23.8 (19.0 to 29.3) | |
| Molecular response of $\leq 0.01\%$ at 48 months | 19.8 (15.3 to 24.9) | 33.0 (27.5 to 38.8) | 29.9 (24.6 to 35.6) | |
| Molecular response of $\leq 0.01\%$ at 60 months | 31.1 (25.7 to 36.8) | 47.9 (41.9 to 53.9) | 43.4 (37.5 to 49.4) | |
| Molecular response of $\leq 0.01\%$ at 72 months | 27.2 (22.1 to 32.8) | 44.3 (38.4 to 50.3) | 45.2 (39.3 to 51.2) | |
| Molecular response of $\leq 0.01\%$ at 84 months | 29.0 (23.8 to 34.6) | 42.9 (37.1 to 48.9) | 40.6 (34.8 to 46.6) | |
| Molecular response of $\leq 0.01\%$ at 96 months | 28.3 (23.1 to 33.9) | 39.7 (34.0 to 45.7) | 38.1 (32.4 to 44.0) | |
| Molecular response of $\leq 0.01\%$ at 108 months | 32.2 (26.7 to 37.9) | 40.4 (34.6 to 46.4) | 34.9 (29.3 to 40.8) | |
| Molecular response of $\leq 0.01\%$ at 120 months | 28.3 (23.1 to 33.9) | 35.5 (29.9 to 41.4) | 33.8 (28.3 to 39.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4.5 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib

| | |
|-----------------|---|
| End point title | Rate of a ≥ 4.5 log reduction in BCR-ABL transcripts in nilotinib treatment arms with imatinib |
|-----------------|---|

End point description:

This is the molecular response of $\leq 0.0032\%$ is defined as BCR-ABL ratio (%) on IS $\leq 0.0032\%$ (corresponds to ≥ 4.5 log reduction of BCR-ABL transcripts from standardized baseline value)

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

End point timeframe:

at 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|--|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Molecular response of $\leq 0.0032\%$ at 6 months | 0.0 (0.0 to 1.3) | 3.5 (1.7 to 6.4) | 1.4 (0.4 to 3.6) | |
| Molecular response of $\leq 0.0032\%$ at 12 months | 0.4 (0.0 to 2.0) | 4.6 (2.5 to 7.8) | 5.0 (2.8 to 8.2) | |
| Molecular response of $\leq 0.0032\%$ at 24 months | 2.8 (1.2 to 5.5) | 12.4 (8.8 to 16.8) | 7.8 (5.0 to 11.6) | |
| Molecular response of $\leq 0.0032\%$ at 36 months | 8.1 (5.2 to 11.9) | 13.8 (10.0 to 18.4) | 12.1 (8.5 to 16.5) | |
| Molecular response of ≤ 0.01032 at 48 months | 10.2 (7.0 to 14.4) | 16.3 (12.2 to 21.2) | 17.1 (12.9 to 22.0) | |

| | | | | |
|---|---------------------|---------------------|---------------------|--|
| Molecular response of $\leq 0.0032\%$ at 60 months | 19.8 (15.3 to 24.9) | 32.3 (26.8 to 38.1) | 29.5 (24.3 to 35.2) | |
| Molecular response of $\leq 0.0032\%$ at 72 months | 18.0 (13.7 to 23.0) | 31.2 (25.8 to 37.0) | 28.8 (23.6 to 34.5) | |
| Molecular response of $\leq 0.0032\%$ at 84 months | 19.1 (14.7 to 24.2) | 31.6 (26.2 to 37.3) | 28.8 (23.6 to 34.5) | |
| Molecular response of $\leq 0.01\%$ at 96 months | 23.3 (18.5 to 28.7) | 31.9 (26.5 to 37.7) | 32.4 (26.9 to 38.2) | |
| Molecular response of $\leq 0.0032\%$ at 108 months | 24.0 (19.2 to 29.4) | 31.9 (26.5 to 37.7) | 28.1 (22.9 to 33.8) | |
| Molecular response of $\leq 0.0032\%$ at 120 months | 21.2 (16.6 to 26.4) | 27.0 (21.9 to 32.5) | 25.6 (20.6 to 31.1) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first MMR

| | |
|---|-------------------|
| End point title | Time to first MMR |
| End point description: | |
| Time to MMR is defined as time from date of randomization to the date of the first documented MMR in nilotinib treatment arms, compared to imatinib in adult patients with Ph+ CML in CP. | |
| End point type | Secondary |
| End point timeframe: | |
| up to 84 months | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 14.13 (11.60 to 17.31) | 8.31 (6.21 to 8.48) | 8.53 (8.31 to 11.07) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of MMR

| | |
|---|-----------------|
| End point title | Duration of MMR |
| End point description: | |
| Duration of MMR for patients with MMR is defined as the time between date of MMR and the earliest of the following: loss of MMR, CML-related death or progression to AP/BC during study treatment The time will be censored at last molecular assessment (PCR) date for patients for whom none of the above events is reported. | |
| End point type | Secondary |
| End point timeframe: | |
| approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

| | |
|--|---|
| End point title | Time to both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts |
| End point description: Time to BCR-ABL ratio of $\leq 0.01\%$ and $\leq 0.0032\%$ is defined as: date of first BCR-ABL ratio of $\leq 0.01\%$ and $\leq 0.0032\%$ - date of randomization +1. | |
| End point type | Secondary |
| End point timeframe: up to 84 months | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|---|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| time to first molecular response of $\leq 0.01\%$ | 30.46 (24.11 to 36.01) | 19.38 (16.62 to 22.34) | 22.70 (19.48 to 27.63) | |
| time to first molecular response of $\leq 0.0032\%$ | 37.29 (33.45 to 41.63) | 32.46 (23.23 to 38.67) | 35.94 (30.39 to 41.00) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts

| | |
|--|---|
| End point title | Duration of both a ≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts |
| End point description: It is defined as the time from the date of first documented BCR-ABL ratio of $\leq 0.01\%$ and $\leq 0.0032\%$ to the earliest of the following: Loss of BCR-ABL ratio of $\leq 0.01\%$ and $\leq 0.0032\%$, respectively, CML- | |

related death or progression to AP/BC during study treatment. The time will be censored at last molecular assessment (PCR) date for patients for whom none of the above events is reported.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|---|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| duration of first molecular response of $\leq 0.01\%$ | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |
| duration of first molecular response of $\leq 0.0032\%$ | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of hematologic response

| | |
|--|------------------------------|
| End point title | Rate of hematologic response |
| End point description: | |
| Rate of hematologic response is defined as the percentage of participants in complete hematologic response (defined as the following present for at least 4 weeks: WBC count $< 10 \times 10^9/L$, Platelet count $< 450 \times 10^9/L$, Basophils $< 5\%$, No blasts and promyelocytes in peripheral blood, Myelocytes + metamyelocytes $< 5\%$ in peripheral blood, No evidence of extramedullary disease, including spleen and liver). | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months, 24 months, Overall (beyond 120 months & up to LPLV) | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|--|---------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Complete hematologic response (CHR) by M12 | 93.3 (89.7 to 95.9) | 90.1 (86.0 to 93.3) | 89.0 (84.7 to 92.4) | |
| CHR by M24 | 93.6 (90.1 to 96.2) | 90.8 (86.8 to 93.9) | 90.4 (86.3 to 93.6) | |
| CHR Overall | 94.0 (90.6 to 96.5) | 92.2 (88.4 to 95.0) | 90.7 (86.7 to 93.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete cytogenic response (CCyR)

| | |
|-----------------|--|
| End point title | Time to Complete cytogenic response (CCyR) |
|-----------------|--|

End point description:

Time to CCyR is defined as the time from the date of randomization to the date of first documented CCyR

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

End point timeframe:

24 months

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.5 (5.8 to 10.9) | 5.7 (5.6 to 5.7) | 5.7 (5.7 to 5.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CCyR

| | |
|-----------------|------------------|
| End point title | Duration of CCyR |
|-----------------|------------------|

End point description:

Duration of CCyR is defined as the time from date of first documented CCyR to the earliest date of loss of CCyR.

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

End point timeframe:

up to 72 months

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

| | |
|---|---------------------------------|
| End point title | Progression-free survival (PFS) |
| End point description: Progression-free survival is defined as the time from the date of randomization to the date of event defined as the first documented disease progression to AP/BC or the date of death from any cause occurring in the core or extension study, or during the follow-up period after discontinuation of core or extension study | |
| End point type | Secondary |
| End point timeframe: approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival (EFS)

| | |
|--|---------------------------|
| End point title | Event-free survival (EFS) |
| End point description: Event-free survival is defined as the time from the date of randomization to the date of first occurrence of any of the following: death due to any cause (if death is the primary reason for discontinuation), progression to AP or BC, loss of PCyR, loss of CCyR, loss of CHR | |
| End point type | Secondary |
| End point timeframe: approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

| | |
|---|-----------------------|
| End point title | Overall survival (OS) |
| End point description: | |
| OS is defined as the time from the date of randomization to the date death. Up to 10 calendar years of follow up from the date when the last patient randomized received the first dose of study drug in all active treatment arms of adult patients with Ph+ CML CP. | |
| End point type | Secondary |
| End point timeframe: | |
| approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual dose-intensity

| | |
|---|-----------------------|
| End point title | Actual dose-intensity |
| End point description: | |
| Actual dose intensity is defined as total dose over time on treatment | |
| End point type | Secondary |
| End point timeframe: | |
| approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|-------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 280 | 279 | 277 | |
| Units: mg/day | | | | |
| median (full range (min-max)) | 400.0 (206 to 800) | 591.1 (186 to 699) | 758.9 (232 to 800) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression to AP/BC

| | |
|--|------------------------------|
| End point title | Time to progression to AP/BC |
| End point description: Time to progression to AP/BC is defined as the time from the date of randomization to the date of event defined as the first documented disease progression to AP/BC or the date of CML related death. | |
| End point type | Secondary |
| End point timeframe: approx. 12 years | |

| End point values | Imatinib 400 mg QD | Nilotinb 300 mg BID | Nilotinib 400 mg BID | |
|----------------------------------|--------------------|---------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 283 | 282 | 281 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 999 (999 to 999) | 999 (999 to 999) | 999 (999 to 999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Cmax at 12 months

| | |
|--|--|
| End point title | Pharmacokinetics as per Cmax at 12 months ^[2] |
| End point description: Cmax is defined as the maximum serum concentration after dose | |
| End point type | Secondary |
| End point timeframe: any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, and 12 hours after dose administration | |

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no plan to report statistical analysis for this endpoint

| End point values | Nilotinib 300 mg BID | Nilotinib 400 mg BID | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: ng/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | 1555 (1340 to 2300) | 1440 (1002 to 2125) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Cmin at 12 months

| | |
|------------------------|--|
| End point title | Pharmacokinetics as per Cmin at 12 months ^[3] |
| End point description: | Cmin is defined as the minimum serum concentration after dose |
| End point type | Secondary |
| End point timeframe: | any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hours, 5 hours, 8 hours, and 12 hours after dose administration |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no plan to report statistical analysis for this endpoint

| End point values | Nilotinib 300 mg BID | Nilotinib 400 mg BID | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: ng/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | 1430 (1250 to 1740) | 915 (752 to 2080) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per Tmax at 12 months

| | |
|------------------------|---|
| End point title | Pharmacokinetics as per Tmax at 12 months ^[4] |
| End point description: | Tmax is defined as the sampling time when maximum measured serum concentration occurs |
| End point type | Secondary |
| End point timeframe: | any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hour |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no plan to report statistical analysis for this endpoint

| End point values | Nilotinib 300 mg BID | Nilotinib 400 mg BID | | |
|---------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: hour (h) | | | | |
| median (inter-quartile range (Q1-Q3)) | 1.47 (0.50 to 2.04) | 1.50 (0.00 to 2.02) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics as per AUC0-last at 12 months

| | |
|-----------------|---|
| End point title | Pharmacokinetics as per AUC0-last at 12 months ^[5] |
|-----------------|---|

End point description:

AUC0 - last is defined as area under concentration-time curve from time zero to the last measurable sample, calculated by log-linear trapezoidal method

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

End point timeframe:

any day after day 8 at pre-dose (0 hour), 1 hour, 2 hours, 3 hour

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no plan to report statistical analysis for this endpoint

| End point values | Nilotinib 300 mg BID | Nilotinib 400 mg BID | | |
|---------------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: h.ng/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | 14446 (12806 to 17411) | 11689 (7925 to 18678) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of hematologic response on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

| | |
|-----------------|--|
| End point title | Rate of hematologic response on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension) |
|-----------------|--|

End point description:

Rate of hematologic response is defined as the percentage of participants in complete hematologic

response (defined as the following present for at least 4 weeks: WBC count <10 x 10⁹/L, Platelet count <450 x 10⁹/L, Basophils <5%, No blasts and promyelocytes in peripheral blood, Myelocytes + metamyelocytes < 5% in peripheral blood, No evidence of extramedullary disease, including spleen and liver).

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Overall (beyond 120 months and up to LPLV) | |

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 83.3 (69.8 to 92.5) | 84.6 (65.1 to 95.6) | 66.7 (9.4 to 99.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of complete cytogenetic response (CCyR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

| | |
|-----------------|--|
| End point title | Rate of complete cytogenetic response (CCyR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension) |
|-----------------|--|

End point description:

Rate of CCyR is defined as the percentage of participants in complete cytogenetic response (CCyR). CCyR is defined as 0% of Ph+ metaphases in the bone marrow.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Overall (beyond 120 months and up to LPLV) | |

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 72.9 (58.2 to 84.7) | 73.1 (52.2 to 88.4) | 66.7 (9.4 to 99.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of major molecular response (MMR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

| | |
|-----------------|--|
| End point title | Rate of major molecular response (MMR) on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension) |
|-----------------|--|

End point description:

Rate of MMR is defined as the percentage of participants in MMR (reduction of ≥ 3 logs in BCR-ABL transcripts compared to the standardized baseline established in IRIS, or $\leq 0.1\%$ BCR-ABL/ABL % by international scale and measured by real-time quantitative polymerase chain reaction (RQ-PCR))

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

End point timeframe:

Overall (beyond 120 months and up to LPLV)

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 64.6 (49.5 to 77.8) | 73.1 (52.2 to 88.4) | 66.7 (9.4 to 99.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of a ≥ 4 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

| | |
|-----------------|---|
| End point title | Rate of a ≥ 4 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension) |
|-----------------|---|

End point description:

Molecular response of $\leq 0.01\%$ is defined as BCR-ABL ratio (%) on IS $\leq 0.01\%$ (corresponds to ≥ 4 log reduction of BCR-ABL transcripts from standardized baseline value)

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

End point timeframe:

Overall (beyond 120 months and up to LPLV)

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 43.8 (29.5 to 58.8) | 57.7 (36.9 to 76.6) | 33.3 (0.8 to 90.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of ≥ 4.5 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension)

| | |
|-----------------|---|
| End point title | Rate of ≥ 4.5 log reduction in BCR-ABL transcripts on nilotinib 400 mg BID therapy after insufficient response during core treatment and switch to extension phase (Extension) |
|-----------------|---|

End point description:

Molecular response of $\leq 0.0032\%$ is defined as BCR-ABL ratio (%) on IS $\leq 0.0032\%$ (corresponds to ≥ 4.5 log reduction of BCR-ABL transcripts from standardized baseline value)

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

End point timeframe:

Overall (beyond 120 months and up to LPLV)

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 35.4 (22.2 to 50.5) | 38.5 (20.2 to 59.4) | 33.3 (0.8 to 90.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of newly observed BCR-ABL mutations in patients post-baseline and correlate with response to treatment with imatinib and nilotinib (Extension)

| | |
|-----------------|---|
| End point title | Presence of newly observed BCR-ABL mutations in patients post-baseline and correlate with response to treatment with imatinib and nilotinib (Extension) |
|-----------------|---|

End point description:

This is the percentage of patients with any emergent mutation on extension treatment. The mutation comprised of T315T, less sensitive to nilotinib, unknown and sensitive to nilotinib.

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

End point timeframe:

Overall (beyond 120 months and up to LPLV)

| End point values | Imatinib 400 mg QD (Treatment taken during core phase) | Nilotinib 300 mg BID (Treatment taken during core phase) | Nilotinib 400 mg BID (Treatment taken during core phase) | |
|-----------------------------------|---|---|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 48 | 26 | 3 | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 20.8 | 11.5 | 33.3 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event (AE) timeframe: Adverse events were collected from first dose of study treatment until end of study treatment plus 28 days post treatment, up to maximum duration of 136.6 months in the Core phase and 121.9 months in the Extension phase.

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 | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Imatinib 400 mg QD |
|-----------------------|--------------------|

Reporting group description:

Patients randomized to this arm were to receive 400 mg imatinib once a day (QD). If the patient required a dose escalation from 400 mg/day, the patient was to receive 400 mg imatinib twice daily orally. Imatinib was taken with food and a large glass of water. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits during the study. In cases of vomiting doses were not to be repeated.

| | |
|-----------------------|----------------------|
| Reporting group title | Nilotinib 300 mg BID |
|-----------------------|----------------------|

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 300 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

| | |
|-----------------------|----------------------|
| Reporting group title | Nilotinib 400 mg BID |
|-----------------------|----------------------|

Reporting group description:

Patients who were randomized to this arm were to receive nilotinib 400 mg twice a day (BID) by mouth each morning and evening approximately 12 hours apart. If the morning or evening dose was delayed for more than 4 hours, the patient was to skip this dose and resume dosing with the next dose as per the original schedule in order to prevent overdosing. No imatinib washout period was necessary prior to administration of nilotinib. Nilotinib was not to be taken with food. No food was to be consumed for at least 2 hours before the dose was taken and no additional oral intake other than water was to be consumed for at least one hour after the dose was taken. Patients were instructed to swallow capsules whole with a full 8 ounce glass of water, and not to chew them. All patients were to avoid grapefruit, star fruit, pomegranate and Seville oranges or juices and products containing these fruits. Vomited doses were not to be repeated.

| | |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All patients randomized in the study to all 3 arms and received at least one dose of study drug.

| Serious adverse events | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID |
|---|---------------------------|-----------------------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 81 / 280 (28.93%) | 106 / 279 (37.99%) | 124 / 277 (44.77%) |
| number of deaths (all causes) | 3 | 10 | 5 |
| number of deaths resulting from adverse events | 0 | 0 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign uterine neoplasm | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blast crisis in myelogenous leukaemia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chloroma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon adenoma | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal stromal tumour | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glioblastoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Histiocytosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leiomyoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukaemic retinopathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Liposarcoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Meningioma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to abdominal wall | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metastases to liver | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metastases to lymph nodes | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metastatic malignant melanoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian epithelial cancer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Pancreatic neuroendocrine tumour | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilloma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraproteinaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostatic adenoma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rosai-Dorfman syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin cancer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superficial spreading melanoma stage III | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Angiopathy | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Aortic aneurysm | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Arterial stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Intermittent claudication | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 279 (1.08%) | 5 / 277 (1.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 8 | 6 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 8 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 8 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Thrombophlebitis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicose vein | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Retained products of conception | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (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 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 2 |

| | | | | |
|---|-----------------|-----------------|-----------------|--|
| Drug interaction | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 | |
| Fatigue | | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Hernia | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Inflammation | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 | |
| Non-cardiac chest pain | | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 3 / 277 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 6 / 279 (2.15%) | 5 / 277 (1.81%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 12 | 2 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adnexa uteri pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast swelling | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gynaecomastia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menstruation irregular | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (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 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scrotal swelling | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine polyp | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 5 / 279 (1.79%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 10 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mediastinal cyst | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Nasal septum deviation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Painful respiration | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Anxiety | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 279 (1.08%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somatic symptom disorder | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Suicidal ideation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blast cell count increased | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Blood creatine phosphokinase MB increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardioactive drug level increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin I increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin T increased | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Urine output decreased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac valve replacement complication | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Chest injury | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gun shot wound | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Heat illness | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incorrect dose administered | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint injury | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Kidney contusion | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament injury | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle rupture | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skeletal injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 compression fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury cervical | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Trisomy 8 | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 5 / 277 (1.81%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 4 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 279 (1.08%) | 10 / 277 (3.61%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 10 | 8 / 30 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 2 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 4 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brugada syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 279 (1.08%) | 10 / 277 (3.61%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 14 / 22 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 6 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 2 / 279 (0.72%) | 6 / 277 (2.17%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | 6 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial ischaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Right ventricular failure | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular arrhythmia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Basilar artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 8 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central nervous system lesion | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar stroke | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Demyelination | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Essential tremor | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Head discomfort | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Headache | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 279 (1.08%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 2 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Migraine | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Miller Fisher syndrome | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy peripheral | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Syncope | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertebral artery stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 2 / 279 (0.72%) | 5 / 277 (1.81%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia macrocytic | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoplastic anaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 3 / 279 (1.08%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 2 / 2 | 6 / 6 | 10 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 4 / 279 (1.43%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 4 / 4 | 8 / 8 | 8 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Otosclerosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blindness unilateral | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Cataract | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular fibrosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Photophobia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Retinopathy | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 5 / 279 (1.79%) | 6 / 277 (2.17%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 12 | 4 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 1 / 279 (0.36%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal inflammation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Ascites | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic gastritis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ischaemic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Constipation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecal vomiting | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric mucosa erythema | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 6 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal stenosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 279 (0.72%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic fistula | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 6 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peptic ulcer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneal haematoma | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 3 / 279 (1.08%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 18 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 3 / 279 (1.08%) | 4 / 277 (1.44%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 6 | 8 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psoriasis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anuria | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bladder obstruction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvi-ureteric obstruction | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal infarct | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Ureterolithiasis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 2 / 279 (0.72%) | 6 / 277 (2.17%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 6 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foot deformity | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma muscle | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 6 / 279 (2.15%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 14 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle spasms | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myofascial pain syndrome | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 279 (0.72%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rotator cuff syndrome | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 ligament ossification | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondyloarthropathy | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Anal infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 2 / 279 (0.72%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Campylobacter gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 2 / 10 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Gastrointestinal viral infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Haematoma infection | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Measles | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Oral infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Osteomyelitis chronic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media chronic | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Perihepatic abscess | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pilonidal cyst | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 280 (2.50%) | 6 / 279 (2.15%) | 6 / 277 (2.17%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 12 | 0 / 16 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| Pneumonia legionella | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salpingitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 1 / 279 (0.36%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 2 / 279 (0.72%) | 0 / 277 (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 |
| Viral rash | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 280 (0.71%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 1 / 279 (0.36%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 1 / 279 (0.36%) | 0 / 277 (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 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 280 (0.00%) | 0 / 279 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 0 / 279 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | All Patients | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 311 / 836 (37.20%) | | |
| number of deaths (all causes) | 18 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Benign uterine neoplasm | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blast crisis in myelogenous leukaemia | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast cancer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chloroma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon adenoma | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 14 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal stromal tumour | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Glioblastoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatocellular carcinoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Histiocytosis | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leiomyoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leukaemic retinopathy | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lipoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Liposarcoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant melanoma in situ | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningioma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to abdominal wall | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to liver | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to lung | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to lymph nodes | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastatic malignant melanoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastatic neoplasm | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ovarian cancer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ovarian epithelial cancer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic carcinoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatic neuroendocrine tumour | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Papilloma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paraproteinaemia | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pituitary tumour benign | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plasma cell myeloma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plasmacytoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate cancer | | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 2 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostatic adenoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal cancer | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rosai-Dorfman syndrome | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin cancer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of skin | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Superficial spreading melanoma stage III | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thyroid cancer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transitional cell carcinoma | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Uterine leiomyoma | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arterial stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 2 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertensive crisis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypotension | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypovolaemic shock | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intermittent claudication | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral arterial occlusive disease | | | | |
| subjects affected / exposed | 8 / 836 (0.96%) | | | |
| occurrences causally related to treatment / all | 14 / 18 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral artery occlusion | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 8 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral artery stenosis | | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 8 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral ischaemia | | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicose vein | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Retained products of conception | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Chest pain | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 2 / 6 | | | |
| deaths causally related to treatment / all | 1 / 3 | | | |
| Drug interaction | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 4 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Generalised oedema | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hernia | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inflammation | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple organ dysfunction syndrome | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Non-cardiac chest pain | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 13 / 836 (1.56%) | | |
| occurrences causally related to treatment / all | 6 / 28 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular stent stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adnexa uteri pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast swelling | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal swelling | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchial obstruction | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 7 / 836 (0.84%) | | | |
| occurrences causally related to treatment / all | 4 / 14 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemothorax | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Interstitial lung disease | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mediastinal cyst | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nasal septum deviation | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Obstructive airways disorder | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Painful respiration | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngeal oedema | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Alcohol withdrawal syndrome | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anxiety | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bipolar disorder | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Completed suicide | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Confusional state | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Depression | | | | |
| subjects affected / exposed | 7 / 836 (0.84%) | | | |
| occurrences causally related to treatment / all | 0 / 14 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mental disorder | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mental status changes | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somatic symptom disorder | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Blast cell count increased | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood alkaline phosphatase increased | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood creatine phosphokinase MB increased | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood creatinine increased | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardioactive drug level increased | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrocardiogram QT prolonged | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gamma-glutamyltransferase increased | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lipase increased | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 4 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Troponin I increased | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Troponin T increased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urine output decreased | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain contusion | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac valve replacement complication | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest injury | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Concussion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gun shot wound | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hand fracture | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 2 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Heat illness | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incorrect dose administered | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intentional overdose | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Jaw fracture | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Joint injury | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Kidney contusion | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ligament injury | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle rupture | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Road traffic accident | | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skeletal injury | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin laceration | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal compression fracture | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord injury cervical | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal fracture | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sternal fracture | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subdural haematoma | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic haemothorax | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular graft occlusion | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Trisomy 8 | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 7 / 836 (0.84%) | | |
| occurrences causally related to treatment / all | 8 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 14 / 836 (1.67%) | | |
| occurrences causally related to treatment / all | 10 / 42 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 6 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| Atrial thrombosis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brugada syndrome | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Cardiac failure congestive | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 4 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardio-respiratory arrest | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiogenic shock | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 14 / 836 (1.67%) | | | |
| occurrences causally related to treatment / all | 14 / 30 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery stenosis | | | | |
| subjects affected / exposed | 4 / 836 (0.48%) | | | |
| occurrences causally related to treatment / all | 6 / 16 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemic cardiomyopathy | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 10 / 836 (1.20%) | | |
| occurrences causally related to treatment / all | 6 / 20 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Basilar artery stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid arteriosclerosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid artery stenosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 836 (0.48%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebellar stroke | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral artery stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 4 / 10 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cerebrovascular disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cervical radiculopathy | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Demyelination | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Essential tremor | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Focal dyscognitive seizures | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head discomfort | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 2 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 2 / 14 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Migraine | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Miller Fisher syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple sclerosis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuralgia | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuropathy peripheral | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parkinson's disease | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parkinsonism | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Polyneuropathy | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sciatica | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Speech disorder | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 6 / 836 (0.72%) | | |
| occurrences causally related to treatment / all | 6 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebral artery stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 836 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia macrocytic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoplastic anaemia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron deficiency anaemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 8 / 836 (0.96%) | | |
| occurrences causally related to treatment / all | 18 / 18 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 10 / 836 (1.20%) | | |
| occurrences causally related to treatment / all | 20 / 20 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Otosclerosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo | | | |
| subjects affected / exposed | 4 / 836 (0.48%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|------------------|--|--|
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blindness unilateral | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cataract | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Macular fibrosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Photophobia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinopathy | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 13 / 836 (1.56%) | | |
| occurrences causally related to treatment / all | 4 / 28 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain lower | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 836 (0.96%) | | |
| occurrences causally related to treatment / all | 0 / 16 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal inflammation | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis ischaemic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspepsia | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enteritis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Faecal vomiting | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Food poisoning | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric mucosa erythema | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorder | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 4 / 836 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 16 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrooesophageal reflux disease | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoidal haemorrhage | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoids | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus paralytic | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incarcerated inguinal hernia | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 836 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mechanical ileus | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 4 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatic fistula | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 8 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 6 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peptic ulcer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periodontal disease | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritoneal haematoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritoneal haemorrhage | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rectal haemorrhage | | | | |
| subjects affected / exposed | 4 / 836 (0.48%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Retroperitoneal haematoma | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal haemorrhage | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 836 (1.08%) | | |
| occurrences causally related to treatment / all | 10 / 20 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 2 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic foot | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 836 (0.48%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anuria | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Azotaemia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder obstruction | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvi-ureteric obstruction | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal infarct | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureterolithiasis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 10 / 836 (1.20%) | | |
| occurrences causally related to treatment / all | 2 / 22 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot deformity | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma muscle | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc protrusion | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 10 / 836 (1.20%) | | |
| occurrences causally related to treatment / all | 0 / 24 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myofascial pain syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 836 (0.48%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal ligament ossification | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondyloarthropathy | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Anal infection | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Campylobacter gastroenteritis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 7 / 836 (0.84%) | | | |
| occurrences causally related to treatment / all | 2 / 16 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epididymitis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia urinary tract infection | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 14 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis salmonella | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal infection | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal viral infection | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| H1N1 influenza | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematoma infection | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected skin ulcer | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Measles | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oral infection | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media chronic | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perihepatic abscess | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 19 / 836 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 44 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Pneumonia legionella | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulpitis dental | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal abscess | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Salpingitis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinusitis | | | | |
| subjects affected / exposed | 3 / 836 (0.36%) | | | |
| occurrences causally related to treatment / all | 2 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Streptococcal sepsis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheobronchitis | | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 5 / 836 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral rash | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gout | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 836 (0.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 836 (0.12%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Imatinib 400 mg QD | Nilotinib 300 mg BID | Nilotinib 400 mg BID |
|---|--------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 274 / 280 (97.86%) | 276 / 279 (98.92%) | 271 / 277 (97.83%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 17 / 280 (6.07%) | 44 / 279 (15.77%) | 55 / 277 (19.86%) |
| occurrences (all) | 34 | 92 | 122 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 40 / 280 (14.29%) | 38 / 279 (13.62%) | 29 / 277 (10.47%) |
| occurrences (all) | 138 | 98 | 84 |
| Chills | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 9 / 280 (3.21%) | 11 / 279 (3.94%) | 14 / 277 (5.05%) |
| occurrences (all) | 22 | 24 | 28 |
| Face oedema | | | |
| subjects affected / exposed | 40 / 280 (14.29%) | 2 / 279 (0.72%) | 7 / 277 (2.53%) |
| occurrences (all) | 114 | 4 | 14 |
| Fatigue | | | |
| subjects affected / exposed | 57 / 280 (20.36%) | 68 / 279 (24.37%) | 56 / 277 (20.22%) |
| occurrences (all) | 136 | 182 | 176 |
| Influenza like illness | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 15 / 279 (5.38%) | 14 / 277 (5.05%) |
| occurrences (all) | 42 | 62 | 50 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 16 / 280 (5.71%) | 16 / 279 (5.73%) | 24 / 277 (8.66%) |
| occurrences (all) | 38 | 40 | 58 |
| Oedema peripheral | | | |
| subjects affected / exposed | 63 / 280 (22.50%) | 32 / 279 (11.47%) | 43 / 277 (15.52%) |
| occurrences (all) | 188 | 82 | 130 |
| Pyrexia | | | |
| subjects affected / exposed | 38 / 280 (13.57%) | 42 / 279 (15.05%) | 49 / 277 (17.69%) |
| occurrences (all) | 110 | 138 | 154 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 41 / 280 (14.64%) | 55 / 279 (19.71%) | 61 / 277 (22.02%) |
| occurrences (all) | 136 | 176 | 180 |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 280 (7.50%) | 33 / 279 (11.83%) | 30 / 277 (10.83%) |
| occurrences (all) | 52 | 82 | 80 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 21 / 280 (7.50%) | 34 / 279 (12.19%) | 29 / 277 (10.47%) |
| occurrences (all) | 72 | 90 | 66 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 26 / 280 (9.29%) | 23 / 279 (8.24%) | 22 / 277 (7.94%) |
| occurrences (all) | 60 | 60 | 52 |
| Depression | | | |

| | | | |
|--------------------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 20 / 280 (7.14%) | 18 / 279 (6.45%) | 18 / 277 (6.50%) |
| occurrences (all) | 50 | 38 | 42 |
| Insomnia | | | |
| subjects affected / exposed | 26 / 280 (9.29%) | 38 / 279 (13.62%) | 37 / 277 (13.36%) |
| occurrences (all) | 60 | 100 | 92 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 25 / 280 (8.93%) | 80 / 279 (28.67%) | 87 / 277 (31.41%) |
| occurrences (all) | 58 | 292 | 364 |
| Amylase increased | | | |
| subjects affected / exposed | 10 / 280 (3.57%) | 22 / 279 (7.89%) | 23 / 277 (8.30%) |
| occurrences (all) | 34 | 70 | 86 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 20 / 280 (7.14%) | 48 / 279 (17.20%) | 44 / 277 (15.88%) |
| occurrences (all) | 50 | 158 | 148 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 12 / 280 (4.29%) | 8 / 279 (2.87%) | 16 / 277 (5.78%) |
| occurrences (all) | 30 | 22 | 40 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 36 / 279 (12.90%) | 41 / 277 (14.80%) |
| occurrences (all) | 10 | 176 | 202 |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 15 / 279 (5.38%) | 15 / 277 (5.42%) |
| occurrences (all) | 2 | 34 | 40 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 21 / 280 (7.50%) | 4 / 279 (1.43%) | 10 / 277 (3.61%) |
| occurrences (all) | 58 | 14 | 32 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 6 / 280 (2.14%) | 9 / 279 (3.23%) | 14 / 277 (5.05%) |
| occurrences (all) | 32 | 28 | 54 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 14 / 280 (5.00%) | 7 / 279 (2.51%) | 15 / 277 (5.42%) |
| occurrences (all) | 46 | 18 | 42 |
| Lipase increased | | | |

| | | | |
|---|--------------------------|--------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 14 / 280 (5.00%) 36 | 37 / 279 (13.26%) 114 | 38 / 277 (13.72%) 188 |
| Weight decreased subjects affected / exposed occurrences (all) | 8 / 280 (2.86%) 16 | 15 / 279 (5.38%) 38 | 13 / 277 (4.69%) 28 |
| Weight increased subjects affected / exposed occurrences (all) | 27 / 280 (9.64%) 66 | 24 / 279 (8.60%) 72 | 22 / 277 (7.94%) 62 |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 4 / 280 (1.43%) 8 | 12 / 279 (4.30%) 38 | 14 / 277 (5.05%) 28 |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 11 / 280 (3.93%) 38 | 18 / 279 (6.45%) 40 | 19 / 277 (6.86%) 48 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 31 / 280 (11.07%) 94 | 34 / 279 (12.19%) 94 | 34 / 277 (12.27%) 82 |
| Headache subjects affected / exposed occurrences (all) | 67 / 280 (23.93%) 224 | 93 / 279 (33.33%) 392 | 105 / 277 (37.91%) 436 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 7 / 280 (2.50%) 18 | 15 / 279 (5.38%) 32 | 10 / 277 (3.61%) 20 |
| Paraesthesia subjects affected / exposed occurrences (all) | 12 / 280 (4.29%) 32 | 14 / 279 (5.02%) 34 | 11 / 277 (3.97%) 28 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 67 / 280 (23.93%) 188 | 38 / 279 (13.62%) 150 | 45 / 277 (16.25%) 132 |
| Leukopenia subjects affected / exposed occurrences (all) | 47 / 280 (16.79%) 198 | 23 / 279 (8.24%) 62 | 22 / 277 (7.94%) 66 |

| | | | |
|--|--------------------------|--------------------------|--------------------------|
| Neutropenia subjects affected / exposed occurrences (all) | 58 / 280 (20.71%) 258 | 44 / 279 (15.77%) 134 | 30 / 277 (10.83%) 92 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 53 / 280 (18.93%) 174 | 54 / 279 (19.35%) 162 | 57 / 277 (20.58%) 180 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 11 / 280 (3.93%) 34 | 13 / 279 (4.66%) 40 | 14 / 277 (5.05%) 44 |
| Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 25 / 280 (8.93%) 80 | 3 / 279 (1.08%) 8 | 5 / 277 (1.81%) 10 |
| Dry eye subjects affected / exposed occurrences (all) | 20 / 280 (7.14%) 44 | 20 / 279 (7.17%) 44 | 21 / 277 (7.58%) 42 |
| Eyelid oedema subjects affected / exposed occurrences (all) | 43 / 280 (15.36%) 114 | 3 / 279 (1.08%) 6 | 5 / 277 (1.81%) 12 |
| Periorbital oedema subjects affected / exposed occurrences (all) | 44 / 280 (15.71%) 106 | 1 / 279 (0.36%) 2 | 4 / 277 (1.44%) 8 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 13 / 280 (4.64%) 34 | 12 / 279 (4.30%) 24 | 15 / 277 (5.42%) 36 |
| Abdominal pain subjects affected / exposed occurrences (all) | 37 / 280 (13.21%) 92 | 43 / 279 (15.41%) 128 | 48 / 277 (17.33%) 116 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 41 / 280 (14.64%) 130 | 51 / 279 (18.28%) 170 | 61 / 277 (22.02%) 178 |
| Constipation subjects affected / exposed occurrences (all) | 26 / 280 (9.29%) 56 | 63 / 279 (22.58%) 168 | 52 / 277 (18.77%) 160 |
| Diarrhoea | | | |

| | | | |
|--|--------------------|-------------------|-------------------|
| subjects affected / exposed | 133 / 280 (47.50%) | 58 / 279 (20.79%) | 67 / 277 (24.19%) |
| occurrences (all) | 552 | 202 | 216 |
| Dyspepsia | | | |
| subjects affected / exposed | 37 / 280 (13.21%) | 32 / 279 (11.47%) | 36 / 277 (13.00%) |
| occurrences (all) | 98 | 90 | 92 |
| Flatulence | | | |
| subjects affected / exposed | 12 / 280 (4.29%) | 12 / 279 (4.30%) | 15 / 277 (5.42%) |
| occurrences (all) | 24 | 30 | 34 |
| Gastritis | | | |
| subjects affected / exposed | 11 / 280 (3.93%) | 9 / 279 (3.23%) | 18 / 277 (6.50%) |
| occurrences (all) | 26 | 20 | 42 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 20 / 280 (7.14%) | 15 / 279 (5.38%) | 17 / 277 (6.14%) |
| occurrences (all) | 50 | 36 | 46 |
| Haemorrhoids | | | |
| subjects affected / exposed | 18 / 280 (6.43%) | 9 / 279 (3.23%) | 19 / 277 (6.86%) |
| occurrences (all) | 48 | 20 | 40 |
| Nausea | | | |
| subjects affected / exposed | 118 / 280 (42.14%) | 61 / 279 (21.86%) | 88 / 277 (31.77%) |
| occurrences (all) | 436 | 290 | 264 |
| Toothache | | | |
| subjects affected / exposed | 18 / 280 (6.43%) | 13 / 279 (4.66%) | 11 / 277 (3.97%) |
| occurrences (all) | 36 | 36 | 26 |
| Vomiting | | | |
| subjects affected / exposed | 79 / 280 (28.21%) | 45 / 279 (16.13%) | 60 / 277 (21.66%) |
| occurrences (all) | 344 | 210 | 204 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 5 / 280 (1.79%) | 53 / 279 (19.00%) | 53 / 277 (19.13%) |
| occurrences (all) | 20 | 218 | 218 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 21 / 280 (7.50%) | 41 / 279 (14.70%) | 58 / 277 (20.94%) |
| occurrences (all) | 42 | 88 | 140 |
| Dry skin | | | |

| | | | |
|---|-------------------|--------------------|--------------------|
| subjects affected / exposed | 17 / 280 (6.07%) | 34 / 279 (12.19%) | 40 / 277 (14.44%) |
| occurrences (all) | 36 | 92 | 102 |
| Eczema | | | |
| subjects affected / exposed | 10 / 280 (3.57%) | 16 / 279 (5.73%) | 11 / 277 (3.97%) |
| occurrences (all) | 28 | 42 | 34 |
| Erythema | | | |
| subjects affected / exposed | 10 / 280 (3.57%) | 15 / 279 (5.38%) | 18 / 277 (6.50%) |
| occurrences (all) | 20 | 32 | 44 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 4 / 280 (1.43%) | 13 / 279 (4.66%) | 16 / 277 (5.78%) |
| occurrences (all) | 10 | 36 | 36 |
| Night sweats | | | |
| subjects affected / exposed | 8 / 280 (2.86%) | 10 / 279 (3.58%) | 18 / 277 (6.50%) |
| occurrences (all) | 20 | 28 | 44 |
| Pruritus | | | |
| subjects affected / exposed | 20 / 280 (7.14%) | 61 / 279 (21.86%) | 56 / 277 (20.22%) |
| occurrences (all) | 46 | 178 | 162 |
| Rash | | | |
| subjects affected / exposed | 57 / 280 (20.36%) | 110 / 279 (39.43%) | 124 / 277 (44.77%) |
| occurrences (all) | 186 | 378 | 480 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 60 / 280 (21.43%) | 72 / 279 (25.81%) | 65 / 277 (23.47%) |
| occurrences (all) | 158 | 220 | 180 |
| Back pain | | | |
| subjects affected / exposed | 54 / 280 (19.29%) | 64 / 279 (22.94%) | 65 / 277 (23.47%) |
| occurrences (all) | 178 | 194 | 178 |
| Bone pain | | | |
| subjects affected / exposed | 16 / 280 (5.71%) | 21 / 279 (7.53%) | 29 / 277 (10.47%) |
| occurrences (all) | 36 | 60 | 60 |
| Muscle spasms | | | |
| subjects affected / exposed | 97 / 280 (34.64%) | 38 / 279 (13.62%) | 37 / 277 (13.36%) |
| occurrences (all) | 370 | 104 | 118 |
| Musculoskeletal pain | | | |

| | | | |
|---|--------------------------|--------------------------|--------------------------|
| subjects affected / exposed occurrences (all) | 24 / 280 (8.57%) 66 | 27 / 279 (9.68%) 78 | 38 / 277 (13.72%) 96 |
| Myalgia subjects affected / exposed occurrences (all) | 56 / 280 (20.00%) 152 | 57 / 279 (20.43%) 146 | 55 / 277 (19.86%) 166 |
| Neck pain subjects affected / exposed occurrences (all) | 8 / 280 (2.86%) 18 | 19 / 279 (6.81%) 44 | 11 / 277 (3.97%) 24 |
| Pain in extremity subjects affected / exposed occurrences (all) | 47 / 280 (16.79%) 122 | 47 / 279 (16.85%) 154 | 52 / 277 (18.77%) 162 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 27 / 280 (9.64%) 82 | 27 / 279 (9.68%) 94 | 19 / 277 (6.86%) 56 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 20 / 280 (7.14%) 50 | 21 / 279 (7.53%) 48 | 18 / 277 (6.50%) 42 |
| Folliculitis subjects affected / exposed occurrences (all) | 3 / 280 (1.07%) 6 | 15 / 279 (5.38%) 34 | 17 / 277 (6.14%) 60 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 30 / 280 (10.71%) 76 | 24 / 279 (8.60%) 56 | 21 / 277 (7.58%) 56 |
| Herpes zoster subjects affected / exposed occurrences (all) | 13 / 280 (4.64%) 28 | 14 / 279 (5.02%) 28 | 8 / 277 (2.89%) 16 |
| Influenza subjects affected / exposed occurrences (all) | 36 / 280 (12.86%) 132 | 45 / 279 (16.13%) 140 | 51 / 277 (18.41%) 154 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 65 / 280 (23.21%) 298 | 81 / 279 (29.03%) 536 | 67 / 277 (24.19%) 396 |
| Pharyngitis subjects affected / exposed occurrences (all) | 15 / 280 (5.36%) 46 | 16 / 279 (5.73%) 44 | 17 / 277 (6.14%) 42 |

| | | | |
|------------------------------------|-------------------|-------------------|-------------------|
| Sinusitis | | | |
| subjects affected / exposed | 20 / 280 (7.14%) | 23 / 279 (8.24%) | 29 / 277 (10.47%) |
| occurrences (all) | 72 | 72 | 104 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 44 / 280 (15.71%) | 56 / 279 (20.07%) | 67 / 277 (24.19%) |
| occurrences (all) | 152 | 226 | 248 |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 280 (4.29%) | 16 / 279 (5.73%) | 27 / 277 (9.75%) |
| occurrences (all) | 54 | 46 | 102 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 13 / 280 (4.64%) | 28 / 279 (10.04%) | 22 / 277 (7.94%) |
| occurrences (all) | 32 | 76 | 54 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 3 / 280 (1.07%) | 33 / 279 (11.83%) | 39 / 277 (14.08%) |
| occurrences (all) | 8 | 78 | 98 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 8 / 280 (2.86%) | 28 / 279 (10.04%) | 28 / 277 (10.11%) |
| occurrences (all) | 24 | 92 | 122 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 280 (0.36%) | 19 / 279 (6.81%) | 15 / 277 (5.42%) |
| occurrences (all) | 2 | 46 | 40 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 5 / 280 (1.79%) | 12 / 279 (4.30%) | 15 / 277 (5.42%) |
| occurrences (all) | 12 | 32 | 38 |
| Hypokalaemia | | | |
| subjects affected / exposed | 15 / 280 (5.36%) | 19 / 279 (6.81%) | 11 / 277 (3.97%) |
| occurrences (all) | 40 | 50 | 40 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 50 / 280 (17.86%) | 45 / 279 (16.13%) | 55 / 277 (19.86%) |
| occurrences (all) | 220 | 166 | 202 |

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | All Patients | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 821 / 836 (98.21%) | | |
| Vascular disorders | | | |

| | | | |
|--|---------------------------|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 116 / 836 (13.88%) 248 | | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 107 / 836 (12.80%) 320 | | |
| Chills subjects affected / exposed occurrences (all) | 34 / 836 (4.07%) 74 | | |
| Face oedema subjects affected / exposed occurrences (all) | 49 / 836 (5.86%) 132 | | |
| Fatigue subjects affected / exposed occurrences (all) | 181 / 836 (21.65%) 494 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 43 / 836 (5.14%) 154 | | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 56 / 836 (6.70%) 136 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 138 / 836 (16.51%) 400 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 129 / 836 (15.43%) 402 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 157 / 836 (18.78%) 492 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 84 / 836 (10.05%) 214 | | |
| Oropharyngeal pain | | | |

| | | | |
|--------------------------------------|--------------------|--|--|
| subjects affected / exposed | 84 / 836 (10.05%) | | |
| occurrences (all) | 228 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 71 / 836 (8.49%) | | |
| occurrences (all) | 172 | | |
| Depression | | | |
| subjects affected / exposed | 56 / 836 (6.70%) | | |
| occurrences (all) | 130 | | |
| Insomnia | | | |
| subjects affected / exposed | 101 / 836 (12.08%) | | |
| occurrences (all) | 252 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 192 / 836 (22.97%) | | |
| occurrences (all) | 714 | | |
| Amylase increased | | | |
| subjects affected / exposed | 55 / 836 (6.58%) | | |
| occurrences (all) | 190 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 112 / 836 (13.40%) | | |
| occurrences (all) | 356 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 36 / 836 (4.31%) | | |
| occurrences (all) | 92 | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 81 / 836 (9.69%) | | |
| occurrences (all) | 388 | | |
| Blood cholesterol increased | | | |
| subjects affected / exposed | 31 / 836 (3.71%) | | |
| occurrences (all) | 76 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 35 / 836 (4.19%) | | |
| occurrences (all) | 104 | | |
| Blood phosphorus decreased | | | |

| | | | |
|--|--------------------|--|--|
| subjects affected / exposed | 29 / 836 (3.47%) | | |
| occurrences (all) | 114 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 36 / 836 (4.31%) | | |
| occurrences (all) | 106 | | |
| Lipase increased | | | |
| subjects affected / exposed | 89 / 836 (10.65%) | | |
| occurrences (all) | 338 | | |
| Weight decreased | | | |
| subjects affected / exposed | 36 / 836 (4.31%) | | |
| occurrences (all) | 82 | | |
| Weight increased | | | |
| subjects affected / exposed | 73 / 836 (8.73%) | | |
| occurrences (all) | 200 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 30 / 836 (3.59%) | | |
| occurrences (all) | 74 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 48 / 836 (5.74%) | | |
| occurrences (all) | 126 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 99 / 836 (11.84%) | | |
| occurrences (all) | 270 | | |
| Headache | | | |
| subjects affected / exposed | 265 / 836 (31.70%) | | |
| occurrences (all) | 1052 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 32 / 836 (3.83%) | | |
| occurrences (all) | 70 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 37 / 836 (4.43%) | | |
| occurrences (all) | 94 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| Anaemia | | | |
| subjects affected / exposed | 150 / 836 (17.94%) | | |
| occurrences (all) | 470 | | |
| Leukopenia | | | |
| subjects affected / exposed | 92 / 836 (11.00%) | | |
| occurrences (all) | 326 | | |
| Neutropenia | | | |
| subjects affected / exposed | 132 / 836 (15.79%) | | |
| occurrences (all) | 484 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 164 / 836 (19.62%) | | |
| occurrences (all) | 516 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 38 / 836 (4.55%) | | |
| occurrences (all) | 118 | | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 33 / 836 (3.95%) | | |
| occurrences (all) | 98 | | |
| Dry eye | | | |
| subjects affected / exposed | 61 / 836 (7.30%) | | |
| occurrences (all) | 130 | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 51 / 836 (6.10%) | | |
| occurrences (all) | 132 | | |
| Periorbital oedema | | | |
| subjects affected / exposed | 49 / 836 (5.86%) | | |
| occurrences (all) | 116 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 40 / 836 (4.78%) | | |
| occurrences (all) | 94 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 128 / 836 (15.31%) | | |
| occurrences (all) | 336 | | |
| Abdominal pain upper | | | |

| | | | |
|----------------------------------|--------------------|--|--|
| subjects affected / exposed | 153 / 836 (18.30%) | | |
| occurrences (all) | 478 | | |
| Constipation | | | |
| subjects affected / exposed | 141 / 836 (16.87%) | | |
| occurrences (all) | 384 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 258 / 836 (30.86%) | | |
| occurrences (all) | 970 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 105 / 836 (12.56%) | | |
| occurrences (all) | 280 | | |
| Flatulence | | | |
| subjects affected / exposed | 39 / 836 (4.67%) | | |
| occurrences (all) | 88 | | |
| Gastritis | | | |
| subjects affected / exposed | 38 / 836 (4.55%) | | |
| occurrences (all) | 88 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 52 / 836 (6.22%) | | |
| occurrences (all) | 132 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 46 / 836 (5.50%) | | |
| occurrences (all) | 108 | | |
| Nausea | | | |
| subjects affected / exposed | 267 / 836 (31.94%) | | |
| occurrences (all) | 990 | | |
| Toothache | | | |
| subjects affected / exposed | 42 / 836 (5.02%) | | |
| occurrences (all) | 98 | | |
| Vomiting | | | |
| subjects affected / exposed | 184 / 836 (22.01%) | | |
| occurrences (all) | 758 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 111 / 836 (13.28%) | | |
| occurrences (all) | 456 | | |

| | | | |
|---|--------------------|--|--|
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 120 / 836 (14.35%) | | |
| occurrences (all) | 270 | | |
| Dry skin | | | |
| subjects affected / exposed | 91 / 836 (10.89%) | | |
| occurrences (all) | 230 | | |
| Eczema | | | |
| subjects affected / exposed | 37 / 836 (4.43%) | | |
| occurrences (all) | 104 | | |
| Erythema | | | |
| subjects affected / exposed | 43 / 836 (5.14%) | | |
| occurrences (all) | 96 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 33 / 836 (3.95%) | | |
| occurrences (all) | 82 | | |
| Night sweats | | | |
| subjects affected / exposed | 36 / 836 (4.31%) | | |
| occurrences (all) | 92 | | |
| Pruritus | | | |
| subjects affected / exposed | 137 / 836 (16.39%) | | |
| occurrences (all) | 386 | | |
| Rash | | | |
| subjects affected / exposed | 291 / 836 (34.81%) | | |
| occurrences (all) | 1044 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 197 / 836 (23.56%) | | |
| occurrences (all) | 558 | | |
| Back pain | | | |
| subjects affected / exposed | 183 / 836 (21.89%) | | |
| occurrences (all) | 550 | | |
| Bone pain | | | |
| subjects affected / exposed | 66 / 836 (7.89%) | | |
| occurrences (all) | 156 | | |
| Muscle spasms | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 172 / 836 (20.57%) | | |
| occurrences (all) | 592 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 89 / 836 (10.65%) | | |
| occurrences (all) | 240 | | |
| Myalgia | | | |
| subjects affected / exposed | 168 / 836 (20.10%) | | |
| occurrences (all) | 464 | | |
| Neck pain | | | |
| subjects affected / exposed | 38 / 836 (4.55%) | | |
| occurrences (all) | 86 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 146 / 836 (17.46%) | | |
| occurrences (all) | 438 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 73 / 836 (8.73%) | | |
| occurrences (all) | 232 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 59 / 836 (7.06%) | | |
| occurrences (all) | 140 | | |
| Folliculitis | | | |
| subjects affected / exposed | 35 / 836 (4.19%) | | |
| occurrences (all) | 100 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 75 / 836 (8.97%) | | |
| occurrences (all) | 188 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 35 / 836 (4.19%) | | |
| occurrences (all) | 72 | | |
| Influenza | | | |
| subjects affected / exposed | 132 / 836 (15.79%) | | |
| occurrences (all) | 426 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 213 / 836 (25.48%) | | |
| occurrences (all) | 1230 | | |

| | | | |
|------------------------------------|--------------------|--|--|
| Pharyngitis | | | |
| subjects affected / exposed | 48 / 836 (5.74%) | | |
| occurrences (all) | 132 | | |
| Sinusitis | | | |
| subjects affected / exposed | 72 / 836 (8.61%) | | |
| occurrences (all) | 248 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 167 / 836 (19.98%) | | |
| occurrences (all) | 626 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 55 / 836 (6.58%) | | |
| occurrences (all) | 202 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 63 / 836 (7.54%) | | |
| occurrences (all) | 162 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 75 / 836 (8.97%) | | |
| occurrences (all) | 184 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 64 / 836 (7.66%) | | |
| occurrences (all) | 238 | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 35 / 836 (4.19%) | | |
| occurrences (all) | 88 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 32 / 836 (3.83%) | | |
| occurrences (all) | 82 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 45 / 836 (5.38%) | | |
| occurrences (all) | 130 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 150 / 836 (17.94%) | | |
| occurrences (all) | 588 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 March 2007 | <p>Amendment 1 (released 20 weeks before first patient first visit on 31-Jul-2007) was a local, country-specific amendment for Japan. The modifications to the protocol were made in order to allow patients in Japan to participate in this global study.</p> <p>Specifically, this study clarified the tablet strength for imatinib and stated that PK parameters in Japanese patients would be investigated more thoroughly. This amendment also indicated that Japan would not be participating in the pharmacogenetic, pharmacogenomic, and biomarker portions of the study. Additionally, changes were made to align study procedures in data review/management and safety monitoring/reporting with Japanese standards of practice.</p> |
| 09 June 2007 | <p>Amendment 2 (released seven weeks before first patient first visit on 31-Jul-2007) was a global amendment to reflect newly available data in support of an alternate nilotinib lower dose and regimen (300 mg bid replaced 600 mg qd). This amendment removed (1) the dose escalation in the nilotinib 300 mg bid arm and (2) the crossover regimens for all arms, while establishing an extension protocol (Protocol post-text supplement 4) to allow for continuation of therapy after patients had demonstrated lack of response to their assigned treatment regimen. Clarifications of the dose escalation in the imatinib arm and the use and definition of MMR in the clinical conduct of the study were also made. Statistically, the protocol was amended to include the following: "durable" MMR to be measured at 24 months, patients with missing data were to be considered as non-responders, confirmed responses for MMR, and the presentation of ≥ 4.5 log reduction in BCR-ABL transcripts.</p> |
| 29 November 2007 | <p>Amendment 3 (released on 29-Nov-2007 after 69 patients were enrolled into the study) was a global amendment. The major changes in this amendment included:</p> <ul style="list-style-type: none">-The dosage form of nilotinib (50 mg capsules) was replaced with 150 mg capsules in the nilotinib 300 mg treatment arm;- Clarifications were made to the dose reduction guidelines for study drug related non-hematological toxicities;- The restriction of using Erythropoiesis Stimulating Agents was removed from the protocol, the use of leukapheresis and hydroxyurea and/or anagrelide was to be permitted during the first month of treatment;- The frequency of the patients' reported outcome assessment was reduced;- The entrance criteria to the extension study were clarified;- The PCR committee was removed from the protocol. <p>Additionally, the ECHO and ECG review processes were clarified as follows: (1). ECHOs were to be reviewed both locally and centrally. Study eligibility and all clinical decisions (including dose-adjustments) were to be based on local ECHO reads. Centrally read ECHO results were to be used for the data analyses; (2) the enrollment of patients had to be based on centrally assessed QTcF time. If one of the three serial ECGs prior to dosing on Day 1 of Cycle 1 showed a QTcF >450 ms by automated reading, an immediate manual central reading had to be requested by calling CRO. The patient was not to be dosed if the average of the manually read ECGs confirmed a QTcF >450 ms.</p> |

| | |
|-----------------|--|
| 21 October 2008 | <p>Amendment 4 (released on 21-Oct-2008, following completion of enrolment on 30-Sep-2008, total 846 patients were enrolled into the study) was a global amendment. Some of the major changes in this amendment included:</p> <ul style="list-style-type: none"> - Cardiac troponin was assessed whenever clinically indicated; - "No MMR at 18 months" and "loss of MMR at any time" were moved from the list of definitions of "treatment failures" to the list of definition of "suboptimal responses"; - "Evidence of clonal evolution" was deleted from the list of AP defining criteria; - The dose reduction guidelines for hypophosphatemia, pancreatitis and QTc prolongation were clarified; - For patients who achieved undetectable BCR-ABL by RQ-PCR due to variability in sample quality and blood cell counts, a repeat assay using more than 10 mL of blood may have been needed to determine whether a $\leq 0.01\%$ and $\leq 0.0032\%$ BCR-ABL/ABL% level was reached. Therefore, collection of 20 mL of blood from these patients for PCR analysis was permitted; - The measurement frequency of glucose, insulin, C-peptide, glycosylated hemoglobin A1c (HbA1c) and lipid panel was modified; - Time to event CRF page was removed from CRF binder since the information on this page can be derived from data collected; - The time points of mandatory manual differential counts were clarified; - The time points of evaluation of cytogenetic response were clarified, bone marrow aspirates and/or biopsies were to be performed at the end of every six cycles until Month 24; - Full PK blood samples could be drawn any day after Day 8 at protocol-defined time points; - The definition of a molecular or cytogenetic response duration, and the definition of loss of a molecular or cytogenetic response were clarified; |
| 08 June 2009 | <p>Amendment 5 (released on 08-Jun-2009) was a local, country-specific amendment for Sweden. This amendment includes all changes introduced with global Amendment 4, except the "evidence of clonal evolution" which remains in the list of AP defining criteria upon request from the Swedish medical products agency.</p> <p>The amendments described above (all introduced before primary analysis database lock on 08-Oct-2009) are not considered to affect the interpretation of study results, as most changes were made to enhance safety monitoring. No changes were made to study end points; however, a sensitivity analysis was added to the planned analyses for progression to AP/BC including clonal evolution as a progression criterion</p> |
| 30 July 2010 | <p>Amendment 6 (released on 30-Jul-2010) was a global amendment. The purpose of this amendment was to: remove the comparison of MMR rates at 12 months between studies CAMN107A2303 and CSTI571K2301 from exploratory objectives, modify the decision algorithm for patients insufficiently responding to their assigned core study treatments, amend the schedule of cytogenetic bone marrow assessments, allow patients who have been dose escalated from imatinib 400 mg QD and did not tolerate 400 mg BID imatinib or reduced dose levels of 600 mg QD imatinib, further dose de-escalation to highest tolerable dose. Patients who do not tolerate 300 mg QD must discontinue treatment, removal of the prohibition on the concurrent use of nilotinib with warfarin or other coumarin derivatives, extend biomarker test sample collection beyond Cycle 12, add ECG with central reading after month 12, remove requirements of collecting pregnancy outcomes from female partners of male patients, integrate into the protocol clarifications from the RAP, implement additional changes in the extension protocol.</p> |
| 11 July 2011 | <p>Amendment 7 (released on 11-July-2011) was a global amendment. The purpose of this amendment was to: modify decision algorithm, combine safety analyses with the annual analyses of the study after the Month 24 analysis time point and to disband DMC if there are no significant new safety findings in the Month 36 analysis, remove PK sample collection at the end of core study visit or early discontinuation visit, to remove time-off data collection at cycle 36 and 48, remove treatment options in the event of early termination of nilotinib 300mg BID arm.</p> |

| | |
|------------------|--|
| 31 January 2012 | <p>Amendment 8 (released on 31-Jan-2012) was a global amendment and major changes included:</p> <ul style="list-style-type: none"> - the duration of the study was extended to 10 calendar years from 15-Oct-2008: date when the last patient randomized to the core study received the first dose of study drug. Therefore, the end of study date or Last Patient Last Visit is projected to be 15-Oct-2018. All end-of-study evaluations for ongoing patients must be completed by this date. This includes survival information follow-up on those patients who have discontinued for reasons other than death. By the end of the study, all patients would have received at least 10 calendar years of treatment or discontinued from the study; - remove the option for patients treated with nilotinib in the core study and experiencing unsatisfactory therapeutic effect to enter the extension study to receive imatinib - the current visit frequency after End of Cycle 60 was revised from every 3 months to every six months for patients in MMR; - Bone marrow biopsy for cytogenetics was no longer required to evaluate response; - Vital sign parameters were reduced to assessments of blood pressure and body weight at each visit; cardiac safety monitoring and laboratory safety assessments were modified, collection of the SF-36 and Fact-Leu questionnaires was extended. |
| 09 August 2013 | <p>Amendment 9 (released on 09-Aug-2013) was a global amendment. The purpose of this amendment was to 1) provide additional guidance for the management of ischemic vascular or ischemic cardiovascular events, 2) outlined acceptable contraception methods for female patients of childbearing potential and revised pregnancy testing and reporting processes and 3) clarified the use of commercial drug supply of imatinib and nilotinib.</p> |
| 03 November 2014 | <p>Amendment 10 (released on 03-Nov-2014) was a global amendment. The purpose of this amendment was to:</p> <ul style="list-style-type: none"> - modify treatment guidelines for patients on the nilotinib 400 mg BID treatment arm in the context of ischemic cardio/vascular events - eliminate the Ischemic Vascular or Ischemic Cardiovascular AE Fax alert form - incorporate nilotinib program-wide language regarding monitoring and treatment of glucose and cholesterol as well as dose reduction guidelines - emphasize the importance of monitoring glucose levels in patients and - provide a harmonization on dose reductions guidelines across Novartis-sponsored Tasigna study protocols |
| 18 April 2016 | <p>Amendment 11 (released on 18-Apr-2016) was a global amendment. The purpose of this amendment was to include hepatitis B virus testing as one of the study procedures, to identify study patients who may be at risk of hepatitis B virus reactivation. Reactivation of hepatitis B virus infection could occur in patients who were chronic carriers of this virus and were receiving a drug of the BCR-ABL TKI class such as nilotinib/imatinib. Some cases involving BCR-ABL TKI resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.</p> |
| 30 March 2017 | <p>Amendment 12 (released on 30-Mar-2017) was a global amendment. The main purpose for the amendment was:</p> <ul style="list-style-type: none"> - To change the source of the Reference Safety Information for Glivec® (imatinib), Novartis has taken the decision to discontinue the use of the Investigator's Brochure for Glivec® (imatinib), since Glivec has been on the market for more than 15 years (first registered in 2001) and has a well-established efficacy/safety profile. The Glivec IB version 19 (dated 21-Jun-2016) is the final IB for the compound. As of the dispatch of the Glivec DSUR 006 in July 2017, the latest approved national/regional product information (e.g. in the EU Summary of Product Characteristics) will serve as the reference safety information (RSI) for the compound. In addition, there is no further global clinical development planned for the compound. - After Cycle 60, all ECG assessments were to be performed and assessed locally. The reference to the central evaluation via vendor (eRT) has been removed from the toxicity guidelines for study drug-related non-hematologic toxicity. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results. |
|---|

Notes: