# Clinical trial results:
# A Phase 3 randomized, double-blind study of induction (daunorubicin/cytarabine) and consolidation (high-dose cytarabine) chemotherapy + midostaurin (PKC412) or placebo in newly diagnosed patients <60 years of age with FLT3-mutated acute myeloid leukemia

## 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.

## Summary

| | |
|---|---|
| EudraCT number | 2006-006852-37 |
| Trial protocol | DE ES AT CZ NL SK HU BE IT FR GB |
| Global end of trial date | 26 March 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 09 April 2023 |
| First version publication date | 09 April 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CPKC412A2301 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00651261 |
| 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.emain@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.emain@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 | 26 March 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improved long-term overall survival (OS) in mutant fms-like tyrosine inase 3 (FLT3)-AML patients.

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 | 08 May 2008 |
| 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 | Australia: 2 |
| Country: Number of subjects enrolled | Austria: 12 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Czechia: 11 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Germany: 305 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Italy: 105 |
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Slovakia: 4 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | United States: 223 |

| | |
|---|---|
| Worldwide total number of subjects | 717 |
| EEA total number of subjects | 479 |

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) | 717 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were enrolled across 13 countries at 177 study centers.

### Pre-assignment

Screening details:

This study comprised of 3 phases: Induction, Consolidation and Continuation phase. The randomization was stratified by FLT3 mutation status.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Induction and Consolidation Chemotherapy Plus Midostaurin |

Arm description:

Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Midostaurin |
| Investigational medicinal product code | PKC412 |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

Induction Phase: 50 mg bid on Days 8-21
Consolidation Phase: 50 mg orally bid on Days 8-21
Continuation Phase: 50 mg bid orally on Days 1-28) for up to 12 cycles of 28 days.

| | |
|---|---|
| Investigational medicinal product name | Daunorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Induction Phase: Daunorubicin 60 mg/m2/day by iv push or short infusion on Days 1−3 for up to 2 cycles

| | |
|---|---|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Induction Phase: Cytarabine 200 mg/m2/day continuous iv infusion on Days 1-7
Consolidation Phase: high dose cytarabine (3000 mg/m2 iv every 12 hours on Days 1, 3, and 5) for up to 4 cycles

| **Arm title** | Induction and Consolidation Chemotherapy Plus Placebo |
|---|---|

Arm description:

Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.

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

Dosage and administration details:

Matching placebo was administered orally via a bid regimen

| Investigational medicinal product name | Daunorubicin |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Induction Phase: Daunorubicin 60 mg/m2/day by iv push or short infusion on Days 1−3 for up to 2 cycles

| Investigational medicinal product name | Cytarabine |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Induction Phase: Cytarabine 200 mg/m2/day continuous iv infusion on Days 1-7
Consolidation Phase: high dose cytarabine (3000 mg/m2 iv every 12 hours on Days 1, 3, and 5) for up to 4 cycles

| **Number of subjects in period 1** | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo |
|---|---|---|
| Started | 360 | 357 |
| Completed | 69 | 52 |
| Not completed | 291 | 305 |
| Pt off-treatment for other complicating disease | 3 | 2 |
| Consent withdrawn by subject | 22 | 40 |
| Disease progression | 58 | 58 |
| Adverse Event | 32 | 22 |
| Death | 18 | 18 |
| Other | 44 | 55 |
| Alternative therapy | 109 | 107 |
| Untreated | 5 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Induction and Consolidation Chemotherapy Plus Midostaurin |
| Reporting group description: | |
| Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily. | |
| Reporting group title | Induction and Consolidation Chemotherapy Plus Placebo |
| Reporting group description: | |
| Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily. | |

| Reporting group values | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | Total |
|---|---|---|---|
| Number of subjects | 360 | 357 | 717 |
| Age Categorical<br>Units: Subjects | | | |
| Age Continuous<br>Units: years | | | |
| median | 47.0 | 48.0 | |
| full range (min-max) | 19 to 59 | 18 to 60 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 186 | 212 | 398 |
| Male | 174 | 145 | 319 |
| FLT3 mutational subtype | | | |
| Mutations in the gene encoding the trans-membrane tyrosine kinase FLT3. FLT3 internal tandem duplications (ITD) mutation which results in a duplication between 3 and greater than 100 amino acids most commonly located in the juxtamembrane region. Tyrosine kinase domain (TKD) point mutations are the remainder of those with FLT3 mutations. FLT3 testing was done centrally. | | | |
| Units: Subjects | | | |
| TKD (No ITD) | 81 | 81 | 162 |
| ITD Allelic ratio <0.7 | 171 | 170 | 341 |
| ITD Allelic ratio >=0.7 | 108 | 106 | 214 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 1 | 1 |
| Asian | 8 | 5 | 13 |
| Black or African American | 8 | 9 | 17 |
| White | 147 | 128 | 275 |
| More than one race | 2 | 1 | 3 |
| Unknown or Not Reported | 195 | 213 | 408 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Induction and Consolidation Chemotherapy Plus Midostaurin |
| Reporting group description: | |
| Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily. | |
| Reporting group title | Induction and Consolidation Chemotherapy Plus Placebo |
| Reporting group description: | |
| Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily. | |

### Primary: Overall survival (OS) - Non-censored at the time of Stem Cell Transplantation (SCT)

| | |
|---|---|
| End point title | Overall survival (OS) - Non-censored at the time of Stem Cell Transplantation (SCT) |
| End point description: | |
| Overall survival (OS) was defined as the time interval from randomization to death from any cause. The median OS with 95% CI was estimated using the Kaplan-Meier method. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 10 years | |

| End point values | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 67.71 (31.54 to 109.7) | 25.59 (18.53 to 42.87) | | |

### Statistical analyses

| Statistical analysis title | Midostaurin vs. Placebo for OS (non-censorring) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1 |

## Secondary: Overall Survival - Censored at the time of SCT

| | |
|---|---|
| End point title | Overall Survival - Censored at the time of SCT |

End point description:

Overall survival (OS) was defined as the time interval from randomization to death from any cause. Any participants who received a stem cell transplant were censored at the time of transplant. The median OS with 95% CI was estimated using the Kaplan-Meier method.

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

End point timeframe:

Up to 10 years

| **End point values** | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 999 (104.8 to 999) | 99 (27.43 to 999) | | |

### Statistical analyses

| **Statistical analysis title** | Midostaurin vs. Placebo (Censored) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 1.07 |

## Secondary: Event free survival (EFS) - non-censored for SCT (Key Secondary endpoint)

| | |
|---|---|
| End point title | Event free survival (EFS) - non-censored for SCT (Key Secondary endpoint) |

End point description:

Event free survival (EFS) was defined as the time from randomization until the earliest qualifying event, including: failure to obtain a complete response (CR) on or before 60 days of initiation of protocol therapy; relapse; or death from any cause. Patients alive and event free at the time of analysis were censored on the date of last clinical assessment. The median EFS with 95% CI was estimated using the Kaplan-Meier method. Due to a higher than expected transplant rate, EFS was promoted to be a key secondary endpoint.

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

End point timeframe:

Up to 10 years

| **End point values** | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.25 (5.45 to 11.07) | 2.99 (1.91 to 5.91) | | |

### Statistical analyses

| **Statistical analysis title** | Midostaurin vs. Placebo - EFS |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 0.94 |

## Secondary: Complete Response Rate (CRR)

| End point title | Complete Response Rate (CRR) |
|---|---|

End point description:

Percentage of participants who achieved a complete response (CR). A CR was defined as normalization of blood counts and a marrow showing less than 5% blasts occurring on or before day 60.

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

End point timeframe:

Induction therapy (up to 60 days)

| **End point values** | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 58.9 | 53.5 | | |

### Statistical analyses

| **Statistical analysis title** | Midostaurin vs. Placebo (CRR) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.073 [1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.13 |

Notes:

[1] - One-sided p-value calculated using Cochran-Mantel-Haenszel test for two proportions adjusted for the FLT3 randomization stratum

## Secondary: Disease-free Survival (DFS) - non-censored at the time of SCT

| End point title | Disease-free Survival (DFS) - non-censored at the time of SCT |
|---|---|

End point description:

Disease free survival (DFS) is defined as the time from documentation of first clinical response (CR) at any time to the first of relapse or death from any cause in participants who achieved a CR.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Up to 10 years | |

| **End point values** | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 26.74 (19.78 to 92.81) | 15.51 (11.33 to 23.46) | | |

**Statistical analyses**

| **Statistical analysis title** | Midostaurin vs. Placebo (DFS) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 0.95 |

**Secondary: Disease-free Survival (DFS) Rate one year after completing the planned continuation phase**

| End point title | Disease-free Survival (DFS) Rate one year after completing the planned continuation phase |
|---|---|
| End point description: | |
| DFS was modified to reflect time from end of continuation to relapse/death from any cause. DFS was assessed for all patients having a CR within 60 days of treatment initiation, and who had completed continuation therapy (i.e. had taken study drug for a minimum of 335 days) and were still in CR. The outcome is presented as an estimated probability without an event at 1 year after completing continuation therapy for subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| one year after completion of continuation therapy | |

| End point values | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 41 | | |
| Units: rate | | | | |
| number (confidence interval 95%) | 0.74 (0.61 to 0.84) | 0.90 (0.76 to 0.96) | | |

**Statistical analyses**

| Statistical analysis title | Midostaurin vs Placebo (FFS rate) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 3.22 |

**Secondary: Stem cell transplantation (SCT) rates - Overall**

| End point title | Stem cell transplantation (SCT) rates - Overall |
|---|---|
| End point description: | |
| Stem cell transplantation rates is defined as to compare the SCT rates whether they are similar in the two treatment groups | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 10 years | |

| End point values | Induction and Consolidation Chemotherapy Plus Midostaurin | Induction and Consolidation Chemotherapy Plus Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 360 | 357 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 60.8 | 55.5 | | |

**Statistical analyses**

| Statistical analysis title | Midostaurin vs. Placebo (SCT) |
|---|---|
| Comparison groups | Induction and Consolidation Chemotherapy Plus Midostaurin v Induction and Consolidation Chemotherapy Plus Placebo |
| Number of subjects included in analysis | 717 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Difference in proportions |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.13 |

## Adverse events information

Timeframe for reporting adverse events:

Only Adverse Events (AEs) occurring after the date of the first study drug intake and up to 30 days after the last study drug intake are reported up to a maximum duration of 10 years.

* In North America, 13 expected AEs had all grades collected. For al

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 | 24.1 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Induction and Consolidation Chemotherapy Plus Midostaurin |

Reporting group description:

Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and midostaurin 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and midostaurin at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of midostaurin 50 mg orally twice daily.

| | |
|---|---|
| Reporting group title | ALL Subjects |

Reporting group description:

This includes all subjects who participated in the trial.

| | |
|---|---|
| Reporting group title | Induction and Consolidation Chemotherapy Plus Placebo |

Reporting group description:

Patients received daunorubicin 60 mg/m^2 by IV push days 1-3 plus cytarabine 200 mg/m^2 IV days 1-7, and placebo 50 mg orally twice daily days 8-21. Participants achieving remission received four 28 day cycles of high dose cytarabine (3000 mg/m^2) days 1, 3, & 5 and placebo at 50 mg orally twice daily days 8-14. Maintenance therapy was given to participants who continued in remission for 12 28-day cycles of placebo 50 mg orally twice daily.

| Serious adverse events | Induction and Consolidation Chemotherapy Plus Midostaurin | ALL Subjects | Induction and Consolidation Chemotherapy Plus Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 172 / 345 (49.86%) | 346 / 680 (50.88%) | 174 / 335 (51.94%) |
| number of deaths (all causes) | 15 | 36 | 21 |
| number of deaths resulting from adverse events | 9 | 16 | 7 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma of liver | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Colon cancer metastatic | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Testicular neoplasm | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 16 / 345 (4.64%) | 20 / 680 (2.94%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 6 / 17 | 8 / 21 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Oophorectomy | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Catheter site erythema | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 7 / 345 (2.03%) | 13 / 680 (1.91%) | 6 / 335 (1.79%) |
| occurrences causally related to treatment / all | 6 / 8 | 15 / 17 | 9 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 6 / 680 (0.88%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 6 | 2 / 4 |
| deaths causally related to treatment / all | 2 / 2 | 4 / 5 | 2 / 3 |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injection site reaction | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis in device | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 4 / 680 (0.59%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 345 (2.61%) | 19 / 680 (2.79%) | 10 / 335 (2.99%) |
| occurrences causally related to treatment / all | 3 / 14 | 5 / 24 | 2 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 3 / 3 | 4 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Unevaluable event | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 4 / 680 (0.59%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 4 / 680 (0.59%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal inflammation | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspiration | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 345 (2.03%) | 10 / 680 (1.47%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 3 / 7 | 5 / 10 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 8 / 345 (2.32%) | 11 / 680 (1.62%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 2 / 8 | 4 / 11 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal pain | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngeal oedema | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 15 / 345 (4.35%) | 27 / 680 (3.97%) | 12 / 335 (3.58%) |
| occurrences causally related to treatment / all | 8 / 17 | 14 / 30 | 6 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 5 / 680 (0.74%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 7 / 345 (2.03%) | 7 / 680 (1.03%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 3 / 7 | 3 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary alveolar haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 3 / 680 (0.44%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachypnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Blood fibrinogen increased | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 9 / 345 (2.61%) | 10 / 680 (1.47%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 9 / 10 | 9 / 11 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 10 / 345 (2.90%) | 14 / 680 (2.06%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 9 / 11 | 11 / 15 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 29 / 345 (8.41%) | 62 / 680 (9.12%) | 33 / 335 (9.85%) |
| occurrences causally related to treatment / all | 20 / 30 | 49 / 67 | 29 / 37 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 24 / 345 (6.96%) | 52 / 680 (7.65%) | 28 / 335 (8.36%) |
| occurrences causally related to treatment / all | 16 / 25 | 40 / 58 | 24 / 33 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prothrombin time prolonged | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 12 / 345 (3.48%) | 21 / 680 (3.09%) | 9 / 335 (2.69%) |
| occurrences causally related to treatment / all | 7 / 12 | 15 / 22 | 8 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 5 / 680 (0.74%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 6 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 8 / 345 (2.32%) | 17 / 680 (2.50%) | 9 / 335 (2.69%) |
| occurrences causally related to treatment / all | 8 / 8 | 15 / 17 | 7 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin T increased | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CD4 lymphocytes decreased | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural bile leak | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation mucositis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 6 / 680 (0.88%) | 5 / 335 (1.49%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 6 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Epidermolysis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 3 / 680 (0.44%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 6 / 345 (1.74%) | 8 / 680 (1.18%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 5 / 6 | 7 / 8 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 7 / 680 (1.03%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 2 / 3 | 7 / 8 | 5 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 345 (0.87%) | 3 / 680 (0.44%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nervous system disorders** | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aphasia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 345 (1.16%) | 7 / 680 (1.03%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 3 / 4 | 5 / 7 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 6 / 680 (0.88%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 6 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuroleptic malignant syndrome | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 4 / 680 (0.59%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (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 |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 7 / 680 (1.03%) | 5 / 335 (1.49%) |
| occurrences causally related to treatment / all | 1 / 2 | 4 / 7 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 9 / 345 (2.61%) | 16 / 680 (2.35%) | 7 / 335 (2.09%) |
| occurrences causally related to treatment / all | 7 / 9 | 13 / 17 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 53 / 345 (15.36%) | 106 / 680 (15.59%) | 53 / 335 (15.82%) |
| occurrences causally related to treatment / all | 33 / 70 | 70 / 134 | 37 / 64 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic infarction | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| External ear pain | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deafness | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye pain | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital oedema | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 345 (1.16%) | 10 / 680 (1.47%) | 6 / 335 (1.79%) |
| occurrences causally related to treatment / all | 1 / 5 | 5 / 11 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal ulcer | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorectal discomfort | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (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 |
| Colitis | | | |
| subjects affected / exposed | 11 / 345 (3.19%) | 21 / 680 (3.09%) | 10 / 335 (2.99%) |
| occurrences causally related to treatment / all | 6 / 11 | 10 / 21 | 4 / 10 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 5 / 680 (0.74%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 345 (2.03%) | 17 / 680 (2.50%) | 10 / 335 (2.99%) |
| occurrences causally related to treatment / all | 6 / 9 | 12 / 19 | 6 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspepsia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eructation | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (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 |
| Ileus paralytic | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 6 / 680 (0.88%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 1 / 2 | 4 / 6 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 345 (1.45%) | 11 / 680 (1.62%) | 6 / 335 (1.79%) |
| occurrences causally related to treatment / all | 6 / 8 | 11 / 14 | 5 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal ulcer | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic colitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salivary gland disorder | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 345 (1.16%) | 10 / 680 (1.47%) | 6 / 335 (1.79%) |
| occurrences causally related to treatment / all | 7 / 8 | 13 / 16 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 6 / 345 (1.74%) | 11 / 680 (1.62%) | 5 / 335 (1.49%) |
| occurrences causally related to treatment / all | 3 / 6 | 7 / 11 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 7 / 680 (1.03%) | 5 / 335 (1.49%) |
| occurrences causally related to treatment / all | 2 / 2 | 5 / 7 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 11 / 345 (3.19%) | 15 / 680 (2.21%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 9 / 13 | 12 / 17 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain of skin | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Exfoliative rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 345 (0.87%) | 3 / 680 (0.44%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 8 / 345 (2.32%) | 10 / 680 (1.47%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 3 / 8 | 3 / 10 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal haemorrhage | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urogenital haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral pain | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gouty arthritis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Back pain | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint effusion | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trismus | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenoviral hepatitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acarodermatitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (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 |
| Anal infection | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 5 / 680 (0.74%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 5 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Candida infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 5 / 680 (0.74%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 5 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 25 / 345 (7.25%) | 38 / 680 (5.59%) | 13 / 335 (3.88%) |
| occurrences causally related to treatment / all | 10 / 28 | 15 / 42 | 5 / 14 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 5 / 680 (0.74%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 6 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 345 (1.74%) | 10 / 680 (1.47%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 2 / 6 | 4 / 11 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium colitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis necroticans | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis Escherichia coli | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (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 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 4 / 680 (0.59%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection fungal | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious colitis | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| Infection | | | |
| subjects affected / exposed | 8 / 345 (2.32%) | 11 / 680 (1.62%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 3 / 8 | 5 / 11 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incision site infection | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lip infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 4 / 680 (0.59%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 5 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nail infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 12 / 345 (3.48%) | 18 / 680 (2.65%) | 6 / 335 (1.79%) |
| occurrences causally related to treatment / all | 5 / 12 | 8 / 18 | 3 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Opportunistic infection | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 5 / 680 (0.74%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 5 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 10 / 345 (2.90%) | 11 / 680 (1.62%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 4 / 10 | 5 / 11 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parotitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 27 / 345 (7.83%) | 55 / 680 (8.09%) | 28 / 335 (8.36%) |
| occurrences causally related to treatment / all | 13 / 30 | 26 / 60 | 13 / 30 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia fungal | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 2 / 680 (0.29%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 19 / 345 (5.51%) | 37 / 680 (5.44%) | 18 / 335 (5.37%) |
| occurrences causally related to treatment / all | 14 / 22 | 27 / 41 | 13 / 19 |
| deaths causally related to treatment / all | 2 / 3 | 4 / 7 | 2 / 4 |
| Rhinitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic infection | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic infection fungal | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 345 (2.03%) | 16 / 680 (2.35%) | 9 / 335 (2.69%) |
| occurrences causally related to treatment / all | 2 / 8 | 7 / 19 | 5 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (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 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 3 / 680 (0.44%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 2 / 680 (0.29%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 3 / 680 (0.44%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vulval abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 4 / 680 (0.59%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 5 / 345 (1.45%) | 8 / 680 (1.18%) | 3 / 335 (0.90%) |
| occurrences causally related to treatment / all | 3 / 6 | 3 / 9 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertriglyceridaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 345 (0.00%) | 1 / 680 (0.15%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 1 / 680 (0.15%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 345 (2.32%) | 13 / 680 (1.91%) | 5 / 335 (1.49%) |
| occurrences causally related to treatment / all | 1 / 8 | 2 / 13 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 345 (0.29%) | 2 / 680 (0.29%) | 1 / 335 (0.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 345 (0.87%) | 3 / 680 (0.44%) | 0 / 335 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 4 / 680 (0.59%) | 2 / 335 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 345 (0.58%) | 6 / 680 (0.88%) | 4 / 335 (1.19%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 6 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Induction and Consolidation Chemotherapy Plus Midostaurin | ALL Subjects | Induction and Consolidation Chemotherapy Plus Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 344 / 345 (99.71%) | 679 / 680 (99.85%) | 335 / 335 (100.00%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 39 / 345 (11.30%) | 81 / 680 (11.91%) | 42 / 335 (12.54%) |
| occurrences (all) | 40 | 86 | 46 |
| Hypertension | | | |
| subjects affected / exposed | 24 / 345 (6.96%) | 43 / 680 (6.32%) | 19 / 335 (5.67%) |
| occurrences (all) | 26 | 46 | 20 |
| Haematoma | | | |
| subjects affected / exposed | 38 / 345 (11.01%) | 76 / 680 (11.18%) | 38 / 335 (11.34%) |
| occurrences (all) | 44 | 86 | 42 |
| Phlebitis superficial | | | |
| subjects affected / exposed | 17 / 345 (4.93%) | 38 / 680 (5.59%) | 21 / 335 (6.27%) |
| occurrences (all) | 18 | 39 | 21 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 245 / 345 (71.01%) | 481 / 680 (70.74%) | 236 / 335 (70.45%) |
| occurrences (all) | 337 | 651 | 314 |
| Chills | | | |
| subjects affected / exposed | 39 / 345 (11.30%) | 72 / 680 (10.59%) | 33 / 335 (9.85%) |
| occurrences (all) | 42 | 78 | 36 |
| Chest pain | | | |
| subjects affected / exposed | 15 / 345 (4.35%) | 33 / 680 (4.85%) | 18 / 335 (5.37%) |
| occurrences (all) | 18 | 37 | 19 |
| Injection site reaction | | | |
| subjects affected / exposed | 25 / 345 (7.25%) | 51 / 680 (7.50%) | 26 / 335 (7.76%) |
| occurrences (all) | 27 | 59 | 32 |
| Pyrexia | | | |
| subjects affected / exposed | 86 / 345 (24.93%) | 167 / 680 (24.56%) | 81 / 335 (24.18%) |
| occurrences (all) | 103 | 197 | 94 |
| Oedema peripheral | | | |
| subjects affected / exposed | 56 / 345 (16.23%) | 118 / 680 (17.35%) | 62 / 335 (18.51%) |
| occurrences (all) | 62 | 136 | 74 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 37 / 345 (10.72%) | 67 / 680 (9.85%) | 30 / 335 (8.96%) |
| occurrences (all) | 39 | 73 | 34 |
| Reproductive system and breast disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 15 / 345 (4.35%) | 36 / 680 (5.29%) | 21 / 335 (6.27%) |
| occurrences (all) | 16 | 39 | 23 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Laryngeal pain | | | |
| subjects affected / exposed | 33 / 345 (9.57%) | 61 / 680 (8.97%) | 28 / 335 (8.36%) |
| occurrences (all) | 37 | 69 | 32 |
| Hypoxia | | | |
| subjects affected / exposed | 11 / 345 (3.19%) | 30 / 680 (4.41%) | 19 / 335 (5.67%) |
| occurrences (all) | 11 | 30 | 19 |
| Epistaxis | | | |
| subjects affected / exposed | 71 / 345 (20.58%) | 129 / 680 (18.97%) | 58 / 335 (17.31%) |
| occurrences (all) | 79 | 147 | 68 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 37 / 345 (10.72%) | 73 / 680 (10.74%) | 36 / 335 (10.75%) |
| occurrences (all) | 40 | 78 | 38 |
| Cough | | | |
| subjects affected / exposed | 53 / 345 (15.36%) | 107 / 680 (15.74%) | 54 / 335 (16.12%) |
| occurrences (all) | 66 | 126 | 60 |
| Pneumonitis | | | |
| subjects affected / exposed | 18 / 345 (5.22%) | 45 / 680 (6.62%) | 27 / 335 (8.06%) |
| occurrences (all) | 19 | 46 | 27 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 21 / 345 (6.09%) | 48 / 680 (7.06%) | 27 / 335 (8.06%) |
| occurrences (all) | 23 | 57 | 34 |
| Insomnia | | | |
| subjects affected / exposed | 36 / 345 (10.43%) | 60 / 680 (8.82%) | 24 / 335 (7.16%) |
| occurrences (all) | 44 | 74 | 30 |
| Depression | | | |
| subjects affected / exposed | 15 / 345 (4.35%) | 44 / 680 (6.47%) | 29 / 335 (8.66%) |
| occurrences (all) | 17 | 49 | 32 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 24 / 345 (6.96%) | 47 / 680 (6.91%) | 23 / 335 (6.87%) |
| occurrences (all) | 26 | 52 | 26 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 33 / 345 (9.57%) | 75 / 680 (11.03%) | 42 / 335 (12.54%) |
| occurrences (all) | 36 | 85 | 49 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 37 / 345 (10.72%) | 77 / 680 (11.32%) | 40 / 335 (11.94%) |
| occurrences (all) | 45 | 90 | 45 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 22 / 345 (6.38%) | 52 / 680 (7.65%) | 30 / 335 (8.96%) |
| occurrences (all) | 26 | 63 | 37 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 102 / 345 (29.57%) | 199 / 680 (29.26%) | 97 / 335 (28.96%) |
| occurrences (all) | 147 | 264 | 117 |
| Activated partial thromboplastin time prolonged | | | |

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|---|---|---|---|
| subjects affected / exposed | 34 / 345 (9.86%) | 61 / 680 (8.97%) | 27 / 335 (8.06%) |
| occurrences (all) | 35 | 64 | 29 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 76 / 345 (22.03%) | 149 / 680 (21.91%) | 73 / 335 (21.79%) |
| occurrences (all) | 105 | 194 | 89 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 51 / 345 (14.78%) | 90 / 680 (13.24%) | 39 / 335 (11.64%) |
| occurrences (all) | 71 | 118 | 47 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 36 / 345 (10.43%) | 78 / 680 (11.47%) | 42 / 335 (12.54%) |
| occurrences (all) | 43 | 89 | 46 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 334 / 345 (96.81%) | 656 / 680 (96.47%) | 322 / 335 (96.12%) |
| occurrences (all) | 388 | 749 | 361 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 319 / 345 (92.46%) | 626 / 680 (92.06%) | 307 / 335 (91.64%) |
| occurrences (all) | 376 | 719 | 343 |
| Platelet count decreased | | | |
| subjects affected / exposed | 328 / 345 (95.07%) | 640 / 680 (94.12%) | 312 / 335 (93.13%) |
| occurrences (all) | 403 | 774 | 371 |
| Weight decreased | | | |
| subjects affected / exposed | 11 / 345 (3.19%) | 28 / 680 (4.12%) | 17 / 335 (5.07%) |
| occurrences (all) | 11 | 28 | 17 |
| Weight increased | | | |
| subjects affected / exposed | 18 / 345 (5.22%) | 26 / 680 (3.82%) | 8 / 335 (2.39%) |
| occurrences (all) | 18 | 26 | 8 |
| Injury, poisoning and procedural complications | | | |
| Radiation mucositis | | | |
| subjects affected / exposed | 132 / 345 (38.26%) | 261 / 680 (38.38%) | 129 / 335 (38.51%) |
| occurrences (all) | 156 | 310 | 154 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 25 / 345 (7.25%) | 53 / 680 (7.79%) | 28 / 335 (8.36%) |
| occurrences (all) | 26 | 58 | 32 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 121 / 345 (35.07%) | 227 / 680 (33.38%) | 106 / 335 (31.64%) |
| occurrences (all) | 165 | 297 | 132 |
| Dysgeusia | | | |
| subjects affected / exposed | 9 / 345 (2.61%) | 26 / 680 (3.82%) | 17 / 335 (5.07%) |
| occurrences (all) | 9 | 27 | 18 |
| Dizziness | | | |
| subjects affected / exposed | 53 / 345 (15.36%) | 103 / 680 (15.15%) | 50 / 335 (14.93%) |
| occurrences (all) | 60 | 115 | 55 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 254 / 345 (73.62%) | 506 / 680 (74.41%) | 252 / 335 (75.22%) |
| occurrences (all) | 310 | 613 | 303 |
| Leukopenia | | | |
| subjects affected / exposed | 94 / 345 (27.25%) | 193 / 680 (28.38%) | 99 / 335 (29.55%) |
| occurrences (all) | 114 | 225 | 111 |
| Lymphopenia | | | |
| subjects affected / exposed | 73 / 345 (21.16%) | 149 / 680 (21.91%) | 76 / 335 (22.69%) |
| occurrences (all) | 97 | 182 | 85 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 14 / 345 (4.06%) | 31 / 680 (4.56%) | 17 / 335 (5.07%) |
| occurrences (all) | 16 | 35 | 19 |
| Vomiting | | | |
| subjects affected / exposed | 209 / 345 (60.58%) | 397 / 680 (58.38%) | 188 / 335 (56.12%) |
| occurrences (all) | 278 | 512 | 234 |
| Diarrhoea | | | |
| subjects affected / exposed | 260 / 345 (75.36%) | 508 / 680 (74.71%) | 248 / 335 (74.03%) |
| occurrences (all) | 349 | 645 | 296 |
| Dyspepsia | | | |
| subjects affected / exposed | 25 / 345 (7.25%) | 47 / 680 (6.91%) | 22 / 335 (6.57%) |
| occurrences (all) | 27 | 51 | 24 |
| Dysphagia | | | |
| subjects affected / exposed | 13 / 345 (3.77%) | 32 / 680 (4.71%) | 19 / 335 (5.67%) |
| occurrences (all) | 14 | 34 | 20 |
| Haemorrhoids | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 35 / 345 (10.14%) | 62 / 680 (9.12%) | 27 / 335 (8.06%) |
| occurrences (all) | 36 | 64 | 28 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 16 / 345 (4.64%) | 37 / 680 (5.44%) | 21 / 335 (6.27%) |
| occurrences (all) | 16 | 43 | 27 |
| Nausea | | | |
| subjects affected / exposed | 282 / 345 (81.74%) | 525 / 680 (77.21%) | 243 / 335 (72.54%) |
| occurrences (all) | 393 | 715 | 322 |
| Stomatitis | | | |
| subjects affected / exposed | 59 / 345 (17.10%) | 94 / 680 (13.82%) | 35 / 335 (10.45%) |
| occurrences (all) | 65 | 104 | 39 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 38 / 345 (11.01%) | 74 / 680 (10.88%) | 36 / 335 (10.75%) |
| occurrences (all) | 43 | 81 | 38 |
| Abdominal pain | | | |
| subjects affected / exposed | 71 / 345 (20.58%) | 158 / 680 (23.24%) | 87 / 335 (25.97%) |
| occurrences (all) | 81 | 178 | 97 |
| Constipation | | | |
| subjects affected / exposed | 59 / 345 (17.10%) | 128 / 680 (18.82%) | 69 / 335 (20.60%) |
| occurrences (all) | 69 | 144 | 75 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 40 / 345 (11.59%) | 82 / 680 (12.06%) | 42 / 335 (12.54%) |
| occurrences (all) | 48 | 95 | 47 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 31 / 345 (8.99%) | 71 / 680 (10.44%) | 40 / 335 (11.94%) |
| occurrences (all) | 34 | 78 | 44 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 36 / 345 (10.43%) | 57 / 680 (8.38%) | 21 / 335 (6.27%) |
| occurrences (all) | 43 | 69 | 26 |
| Dermatitis exfoliative | | | |
| subjects affected / exposed | 218 / 345 (63.19%) | 440 / 680 (64.71%) | 222 / 335 (66.27%) |
| occurrences (all) | 269 | 544 | 275 |
| Petechiae | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 88 / 345 (25.51%) | 156 / 680 (22.94%) | 68 / 335 (20.30%) |
| occurrences (all) | 102 | 180 | 78 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 21 / 345 (6.09%) | 32 / 680 (4.71%) | 11 / 335 (3.28%) |
| occurrences (all) | 23 | 34 | 11 |
| Arthralgia | | | |
| subjects affected / exposed | 39 / 345 (11.30%) | 57 / 680 (8.38%) | 18 / 335 (5.37%) |
| occurrences (all) | 44 | 70 | 26 |
| Back pain | | | |
| subjects affected / exposed | 58 / 345 (16.81%) | 100 / 680 (14.71%) | 42 / 335 (12.54%) |
| occurrences (all) | 67 | 118 | 51 |
| Bone pain | | | |
| subjects affected / exposed | 24 / 345 (6.96%) | 47 / 680 (6.91%) | 23 / 335 (6.87%) |
| occurrences (all) | 29 | 56 | 27 |
| Myalgia | | | |
| subjects affected / exposed | 19 / 345 (5.51%) | 38 / 680 (5.59%) | 19 / 335 (5.67%) |
| occurrences (all) | 24 | 45 | 21 |
| Pain in extremity | | | |
| subjects affected / exposed | 32 / 345 (9.28%) | 56 / 680 (8.24%) | 24 / 335 (7.16%) |
| occurrences (all) | 38 | 66 | 28 |
| Infections and infestations | | | |
| Neutropenic infection | | | |
| subjects affected / exposed | 11 / 345 (3.19%) | 28 / 680 (4.12%) | 17 / 335 (5.07%) |
| occurrences (all) | 11 | 28 | 17 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 20 / 345 (5.80%) | 35 / 680 (5.15%) | 15 / 335 (4.48%) |
| occurrences (all) | 28 | 45 | 17 |
| Device related infection | | | |
| subjects affected / exposed | 53 / 345 (15.36%) | 93 / 680 (13.68%) | 40 / 335 (11.94%) |
| occurrences (all) | 61 | 105 | 44 |
| Conjunctivitis | | | |
| subjects affected / exposed | 22 / 345 (6.38%) | 39 / 680 (5.74%) | 17 / 335 (5.07%) |
| occurrences (all) | 22 | 42 | 20 |
| Oral herpes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 345 (4.06%) | 31 / 680 (4.56%) | 17 / 335 (5.07%) |
| occurrences (all) | 15 | 37 | 22 |
| Pneumonia | | | |
| subjects affected / exposed | 28 / 345 (8.12%) | 60 / 680 (8.82%) | 32 / 335 (9.55%) |
| occurrences (all) | 29 | 63 | 34 |
| Urinary tract infection | | | |
| subjects affected / exposed | 16 / 345 (4.64%) | 42 / 680 (6.18%) | 26 / 335 (7.76%) |
| occurrences (all) | 16 | 43 | 27 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 45 / 345 (13.04%) | 103 / 680 (15.15%) | 58 / 335 (17.31%) |
| occurrences (all) | 50 | 116 | 66 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 69 / 345 (20.00%) | 136 / 680 (20.00%) | 67 / 335 (20.00%) |
| occurrences (all) | 79 | 155 | 76 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 66 / 345 (19.13%) | 129 / 680 (18.97%) | 63 / 335 (18.81%) |
| occurrences (all) | 81 | 150 | 69 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 22 / 345 (6.38%) | 38 / 680 (5.59%) | 16 / 335 (4.78%) |
| occurrences (all) | 29 | 50 | 21 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 75 / 345 (21.74%) | 139 / 680 (20.44%) | 64 / 335 (19.10%) |
| occurrences (all) | 109 | 195 | 86 |
| Hypokalaemia | | | |
| subjects affected / exposed | 92 / 345 (26.67%) | 191 / 680 (28.09%) | 99 / 335 (29.55%) |
| occurrences (all) | 110 | 224 | 114 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 36 / 345 (10.43%) | 76 / 680 (11.18%) | 40 / 335 (11.94%) |
| occurrences (all) | 37 | 84 | 47 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 28 / 345 (8.12%) | 62 / 680 (9.12%) | 34 / 335 (10.15%) |
| occurrences (all) | 34 | 74 | 40 |
| Hyponatraemia | | | |
| subjects affected / exposed | 60 / 345 (17.39%) | 120 / 680 (17.65%) | 60 / 335 (17.91%) |
| occurrences (all) | 66 | 131 | 65 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 February 2009 | Clarification of eligibility criterion for patients with neurologic symptoms; Changes in dose modification required in cases of QTc prolongation between 470 ms and 500 ms; Added dose modification requirement for cases of ≥grade-2 neurotoxicity due to high-dose cytarabine |
| 01 April 2009 | Change in dosing regimen for midostaurin/placebo continuation therapy from 14 days of each 28 day cycle to continuous daily dosing, continuing for 12 cycles, along with clarifying rationale; Adding dose modification requirement for cases of QTc prolongation; Clarifying dose modification requirements for nonhematologic toxicities of grade 3/4 severity; Change in prohibited ancillary therapy (i.e. use of aprepitant was not permitted) |
| 01 December 2009 | Changes in reporting of AEs for NNA sites as well as for their expedited reporting requirements; Addition of collection of concomitant medications; Revised information regarding drug accountability, storage and stability, and unblinding of midostaurin; Revision on statistical analyses to be performed for secondary endpoints; Revision on requirement for bone marrow aspiration during remission induction stage and response assessments. |
| 15 December 2010 | At the time of protocol version 1, the transplantation option was estimated to be available for about 15% of the population eligible for the study. This rate of withdrawal from study treatment for patients in first CR was factored into the estimate of sample size. At Amendment 4, based on blinded data from the study to date, 25% of all randomized patients were expected to have received an SCT. The sample size and power justification were therefore revised and justification for amending statistical considerations was added to reflect revised sample size; Addition of a new secondary objective to compare the OS in the two groups using an analysis in which patient who receive an SCT are censored at the time of transplantation. |
| 15 May 2011 | Revision of response assessment to include time requirement for bone marrow aspiration after recovery of ANC and platelet count to document complete response |
| 15 September 2011 | Changes in AE reporting for NA and NNA sites |
| 15 November 2011 | Update in administrative procedure for the unblinding of patients |
| 05 May 2013 | Editorial / Administrative changes |
| 15 February 2015 | Editorial / Administrative changes |
| 15 June 2015 | The protocol was amended to perform the final confirmatory analysis with a DCO of 01-Apr-2015 without waiting for the originally targeted 509 OS events to occur; The secondary endpoint EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint is significant. In addition, the SCT rate was added as a secondary efficacy endpoint. |

| | |
|---|---|
| 27 December 2018 | Data submission for this study will now be performed using Medidata Rave; Adverse event reporting have been updated to reflect the use of CTCAE version 5.0 for serious adverse event reporting; Administrative changes |

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: