

**Clinical trial results:**

A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for Induction and intermediate dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed subjects with FLT-3 mutation negative acute myeloid leukemia (AML)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate.

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2017-003540-21 |
| Trial protocol | DE BE IT PT FR NO ES AT HU BG PL |
| Global end of trial date | 12 February 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 01 March 2022 |
| First version publication date | 01 March 2022 |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | CPKC412E2301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02913261 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

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

| |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 February 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves event free survival (EFS) in subjects with newly diagnosed FLT3-MN (signal ratio (SR) <0.05) AML.

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 | 20 July 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Austria: 14 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | Bulgaria: 2 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | France: 31 |
| Country: Number of subjects enrolled | Germany: 165 |
| Country: Number of subjects enrolled | Israel: 7 |
| Country: Number of subjects enrolled | Italy: 79 |
| Country: Number of subjects enrolled | Japan: 29 |
| Country: Number of subjects enrolled | Norway: 7 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Portugal: 11 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Spain: 63 |
| Country: Number of subjects enrolled | Switzerland: 17 |
| Country: Number of subjects enrolled | Taiwan: 11 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects | 501 |
| EEA total number of subjects | 396 |

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) | 358 |
| From 65 to 84 years | 143 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Five hundred and three participants were randomized. However, the data analysis was considered for 501 participants only (250 participants in midostaurin arm and 251 participants in placebo arm).

Pre-assignment

Screening details:

Participants had to sign informed consent form before screening for enrollment. Participants started chemotherapy at day 1 and were randomized at day 8.

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, Carer, Assessor |

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Midostaurin + chemotherapy |

Arm description:

Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

| | |
|--|---------------|
| 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:

50 mg twice daily

| | |
|--|----------------------------|
| Investigational medicinal product name | Chemotherapy: daunorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

60 mg/m²/d, day 1 -3 (induction 1), 50 mg/m²/d, day 1 -3 (induction 2)

| | |
|--|---------------------------------|
| Investigational medicinal product name | Chemotherapy: cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg/m²/d, days 1 -7 (induction 1), 1.5 g/m²/day, q12h, day 1 -3 (induction 2 & Consolidation)

| | |
|--|---------------------------------|
| Investigational medicinal product name | Chemotherapy: idarubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 12 mg/m ² /d, day 1 -3 (induction 1), 10 mg/m ² /d, day 1 -3 (induction 2) | |
| Arm title | Placebo + chemotherapy |

Arm description:

Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

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

Dosage and administration details:

50 mg twice daily

| | |
|--|----------------------------|
| Investigational medicinal product name | Chemotherapy: daunorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

60 mg/m²/d, day 1 -3 (induction 1), 50 mg/m²/d, day 1 -3 (induction 2)

| | |
|--|---------------------------------|
| Investigational medicinal product name | Chemotherapy: cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg/m²/d, days 1 -7 (induction 1), 1.5 g/m²/day, q12h, day 1 -3 (induction 2 & Consolidation)

| | |
|--|---------------------------------|
| Investigational medicinal product name | Chemotherapy: idarubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

12 mg/m²/d, day 1 -3 (induction 1), 10 mg/m²/d, day 1 -3 (induction 2)

| Number of subjects in period 1 | Midostaurin + chemotherapy | Placebo + chemotherapy |
|---------------------------------------|----------------------------|------------------------|
| Started | 250 | 251 |
| Treated with Midostaurin/Placebo | 245 | 249 |
| Completed | 2 | 1 |
| Not completed | 248 | 250 |

| | | |
|---------------------------------------|----|----|
| Adverse event, serious fatal | 14 | 9 |
| Physician decision | 60 | 60 |
| Terminated by Sponsored | 46 | 50 |
| Subject Decision | 15 | 12 |
| Adverse event, non-fatal | 30 | 34 |
| Failure to meet Continuation Criteria | 24 | 28 |
| Withdrawal of informed consent | 20 | 14 |
| Missing | 3 | 13 |
| Guardian decision | 1 | 1 |
| Lack of efficacy | 19 | 11 |
| New Therapy for Study Indication | 16 | 16 |
| Protocol deviation | - | 2 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------|
| Reporting group title | Midostaurin + chemotherapy |
| Reporting group description: | |
| Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation. | |
| Reporting group title | Placebo + chemotherapy |
| Reporting group description: | |
| Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation. | |

| Reporting group values | Midostaurin + chemotherapy | Placebo + chemotherapy | Total |
|--|----------------------------|------------------------|-------|
| Number of subjects | 250 | 251 | 501 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 182 | 176 | 358 |
| From 65-84 years | 68 | 75 | 143 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| median | 58.0 | 58.0 | |
| full range (min-max) | 19.0 to 78.0 | 18.0 to 79.0 | - |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 122 | 106 | 228 |
| Male | 128 | 145 | 273 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 213 | 208 | 421 |
| Black or African American | 1 | 2 | 3 |
| Asian | 22 | 22 | 44 |
| Multiple | 1 | 1 | 2 |
| Missing | 13 | 18 | 31 |
| ECOG performance status | | | |
| Units: Subjects | | | |
| 0 Status | 119 | 119 | 238 |

| | | | |
|----------------|-----|-----|-----|
| 1 Status | 107 | 115 | 222 |
| 2 Status | 18 | 13 | 31 |
| 3 Status | 2 | 0 | 2 |
| Missing Status | 4 | 4 | 8 |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | Midostaurin + chemotherapy |
| Reporting group description: Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation. | |
| Reporting group title | Placebo + chemotherapy |
| Reporting group description: Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation. | |
| Subject analysis set title | CGP52421 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |
| Subject analysis set title | CGP62221 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |
| Subject analysis set title | CGP52421 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |
| Subject analysis set title | CGP62221 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |
| Subject analysis set title | GCP62221 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |
| Subject analysis set title | GCP52421 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Active Midostaurin metabolite | |

Primary: Event Free Survival (EFS)

| | |
|---|---------------------------|
| End point title | Event Free Survival (EFS) |
| End point description: EFS was defined as the time from randomization to failure to obtain a complete remission (CR) or Complete remission with incomplete hematologic recovery (CRi) with adequate blood count recovery in induction, relapse after CR or CRi with adequate blood count recovery or death due to any cause, whichever occurred first as assessed by the investigator. | |
| End point type | Primary |
| End point timeframe: From date of Randomization up to approx. 30 months | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.98 (2.33 to 8.97) | 5.88 (3.65 to 7.52) | | |

Statistical analyses

| Statistical analysis title | for EFS |
|---|---|
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.0239 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.31 |

Secondary: Overall survival (OS) (Key Secondary)

| | |
|------------------------|--|
| End point title | Overall survival (OS) (Key Secondary) |
| End point description: | OS was defined as the time from randomization to date of death due to any cause. Patients entered the survival follow-up phase once they completed the safety follow up period (30 days after the last dose of midostaurin/placebo) in case of induction failure or if they had relapsed during post-treatment follow-up. Patients were then contacted by telephone every 3 months +/- 2 weeks or had a visit to follow up on their survival status, per Kaplan-Meier estimates. |
| End point type | Secondary |
| End point timeframe: | Between randomization to date of death up to approx. 30 months |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99 (15.54 to 999) | 19.22 (13.8 to 999) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | For OS |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8728 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.29 |

Secondary: Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery (CRi) but with adequate blood count recovery rate.

| | |
|-----------------|--|
| End point title | Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery (CRi) but with adequate blood count recovery rate. |
|-----------------|--|

End point description:

Assessment was based on the International Working Group (IWG) criteria for AML as per investigator assessment.

CR: Bone marrow: < 5% blasts

no blasts with Auer rods; Peripheral blood: neutrophils $\geq 1.0 \times 10^9/L$

platelets $\geq 100 \times 10^9/L$, no blasts; No evidence of extramedullary disease (such as central nervous system (CNS) or soft tissue involvement); Transfusion independent.

CRi with adequate blood count recovery is defined as the following:

Bone marrow

< 5% blasts

no blasts with Auer rods

Peripheral blood

Neutrophils $\geq 1.0 \times 10^9/L$ and $50 \times 10^9/L \leq$ platelets $< 100 \times 10^9/L$

no blasts

No evidence of extramedullary disease (such as CNS or soft tissue involvement).

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

End point timeframe:

At maximum 93 days from induction therapy start

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|-----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 59.2 (52.8 to 65.4) | 61.0 (54.6 to 67.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Minimal Residual Disease (MRD) negative status

| | |
|-----------------|--|
| End point title | Percentage of participants with Minimal Residual Disease (MRD) negative status |
|-----------------|--|

End point description:

Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).

MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

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

End point timeframe:

Between start and three months after end of treatment

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|-----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 40.8 | 41.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase

| | |
|-----------------|--|
| End point title | Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase |
|-----------------|--|

End point description:

MRD- rate was defined as the rate of participants reaching MRD at any timepoint during Post-consolidation phase. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).

MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Between start and three months after end of treatment | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|-----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 27 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 33.3 | 33.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Measurable Residual Disease (MRD) negativity by flow cytometry

| | |
|-----------------|--|
| End point title | Time to Measurable Residual Disease (MRD) negativity by flow cytometry |
|-----------------|--|

End point description:

Time to MRD- is defined as time from randomization to first occurrence of MRD-. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).

MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From date of Randomization up to approx. 17 months | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 2.27 (1.61 to 5.68) | 2.07 (1.68 to 6.80) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival (DFS)

| | |
|-----------------|-----------------------------|
| End point title | Disease-free survival (DFS) |
|-----------------|-----------------------------|

End point description:

DFS as measured from the date of first CR or CRi with adequate blood count recovery to relapse or death due to any cause, whichever occurred first. Participants who did not relapse nor die were censored at the last adequate response assessment. Assessment was based on the IWG criteria for AML as per investigator assessment

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

End point timeframe:

From date of CR or CRi with adequate blood count recovery up to approx. 30 months

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 148 | 153 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 10.5 (7.59 to 99) | 9.1 (6.87 to 12.02) | | |

Statistical analyses

| Statistical analysis title | For DFS |
|---|---|
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.63 |

Secondary: Cumulative incidence of relapse (CIR)

| | |
|-----------------|---------------------------------------|
| End point title | Cumulative incidence of relapse (CIR) |
|-----------------|---------------------------------------|

End point description:

Cumulative Incidence of Relapse (CIR) was defined for participants with CR or CRi with adequate blood count recovery and was the time from achieving the CR or CRi with adequate blood count recovery until the onset of relapse from CR or CRi with adequate blood recovery. Participants without relapse were censored at the last adequate response assessment. Participants who died without relapse were counted as a competing cause of failure.

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

End point timeframe:

From date of CR or CRi with adequate blood count recovery up to approx. 30 months

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 148 | 153 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 5.1 (2.83 to 7.56) | 6.6 (4.99 to 8.77) | | |

Statistical analyses

| Statistical analysis title | For CIR |
|---|---|
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.5866 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 2.87 |

Secondary: Cumulative incidence of death (CID)

| | |
|------------------------|--|
| End point title | Cumulative incidence of death (CID) |
| End point description: | Cumulative Incidence of Death (CID) was defined for all participants achieving CR or CRi with adequate blood count recovery measured from the date of achievement of CR or CRi until the date of death due to any reason. Participants not known to have died were censored on the last contact date. Participants who experienced relapse were counted as a competing cause of failure. |
| End point type | Secondary |
| End point timeframe: | From date of CR or CRi with adequate blood count recovery up to approx. 30 months |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 148 | 153 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 99 (18.00 to 999) | 99 (14.42 to 999) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | For CID |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7937 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 1.54 |

Secondary: Time to CR or CRi with adequate blood count recovery

| | |
|--|--|
| End point title | Time to CR or CRi with adequate blood count recovery |
| End point description: Time to CR or CRi with adequate blood count recovery was defined as the time from randomization to CR or CRi with adequate blood count recovery whichever occurred first | |
| End point type | Secondary |
| End point timeframe: At maximum 93 days from induction therapy start | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 1.12 (1.02 to 1.41) | 1.15 (1.05 to 1.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to partial and full neutrophil recovery

| | |
|--|--|
| End point title | Time to partial and full neutrophil recovery |
| End point description: The time to neutrophil recovery was assessed for the following criteria: number of days from start of treatment to the first day neutrophils $\geq 0.5 \times 10^9/L$, Number of days from start of treatment to the first day neutrophils $\geq 1.0 \times 10^9/L$ | |
| End point type | Secondary |
| End point timeframe: At maximum 93 days from induction therapy start | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Partial neutrophil recovery | 1.1 (0.82 to 1.15) | 0.9 (0.79 to 1.12) | | |
| Full neutrophil recovery | 1.2 (1.05 to 1.48) | 1.1 (0.95 to 1.35) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | For neutrophil recovery - Pbo |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.14 |

| | |
|---|---|
| Statistical analysis title | For neutrophil recovery |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.16 |

Secondary: Time to partial and full platelet recovery

| | |
|-----------------|--|
| End point title | Time to partial and full platelet recovery |
|-----------------|--|

End point description:

Time to platelet recovery was assessed for the following criteria: number of days from start of treatment to the first day platelets $\geq 50 \times 10^9/L$ (partial platelet recovery), number of days from start of treatment to the first day platelets $\geq 100 \times 10^9/L$ (full platelet recovery).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At maximum 93 days from induction therapy start | |

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|----------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Partial platelet recovery | 99 (1.45 to 999) | 99 (3.5 to 999) | | |
| Full platelet recovery | 0.953 (0.89 to 1.12) | 0.887 (0.85 to 0.92) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | For platelet recovery |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.52 |

| | |
|---|---|
| Statistical analysis title | For platelet recovery - Pbo |
| Comparison groups | Midostaurin + chemotherapy v Placebo + chemotherapy |
| Number of subjects included in analysis | 501 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1 |

Secondary: AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

| | |
|-----------------|--|
| End point title | AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 ^[1] |
|-----------------|--|

End point description:

The AUC from time zero to a measurable concentration sampling time (t) (mass x time x volume-1).
Note: as the last sampling time was at 12 h, AUC0-12h was determined after the first dose, reported at Cycle 1, Day 8

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

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

| End point values | Midostaurin + chemotherapy | CGP52421 | CGP62221 | |
|---|----------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 20 | 27 | 27 | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 14800 (± 37.5) | 712 (± 78.4) | 1830 (± 135) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221

| | |
|-----------------|---|
| End point title | Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221 ^[2] |
|-----------------|---|

End point description:

Serial pharmacokinetics (PK) samples were collected in all participants to assess the plasma concentrations of midostaurin, CGP52421 and CGP622.

Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 were measured using a validated liquid chromatography-tandem mass spectrometry (LC- MS/MS) assay and reported at Cycle 1, Day 8

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

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

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

| End point values | Midostaurin + chemotherapy | CGP52421 | CGP62221 | |
|-----------------------------|----------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | 0 ^[5] | |
| Units: ng/mL | | | | |

Notes:

[3] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value

[4] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value

[5] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

| | |
|-----------------|---|
| End point title | AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 ^[6] |
|-----------------|---|

End point description:

The AUC from time zero to the last measurable concentration sampling time after the first dose reported at Cycle 1, Day 8

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

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

| End point values | Midostaurin + chemotherapy | CGP52421 | CGP62221 | |
|---|----------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 27 | 27 | |
| Units: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 12200 (± 59.6) | 493 (± 139) | 1130 (± 249) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

| | |
|-----------------|--|
| End point title | Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 ^[7] |
|-----------------|--|

End point description:

The maximum (peak) observed plasma drug concentration after the first dose administration reported at Cycle 1, Day 8

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

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

| End point values | Midostaurin + chemotherapy | CGP52421 | GCP62221 | |
|---|----------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 27 | 27 | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 1910 (\pm 37.8) | 74.7 (\pm 72.3) | 183 (\pm 128) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

| | |
|-----------------|--|
| End point title | Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221 ^[8] |
|-----------------|--|

End point description:

The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration reported at Cycle 1, Day 8

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

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned for this endpoint

| End point values | Midostaurin + chemotherapy | CGP62221 | GCP52421 | |
|---|----------------------------|----------------------|----------------------|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 | 27 | 27 | |
| Units: hour (hr) | | | | |
| geometric mean (geometric coefficient of variation) | 3.28 (\pm 101) | 7.17 (\pm 57.8) | 5.38 (\pm 89.9) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

| | |
|-----------------|---|
| End point title | Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) |
|-----------------|---|

End point description:

The total FACT-Leu score consists of 44 items with total scores ranging from 0 to 176. Higher scores indicate better HRQoL. Negative changes from baseline indicate a worsening of HRQoL while positive changes indicate an improvement in HRQoL.

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

End point timeframe:

From date of Randomization up to approx. 18 months

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|--------------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 225, 223) | 122.8 (± 22.64) | 123.1 (± 21.21) | | |
| Induction Phase (n = 137, 147) | 123.9 (± 21.50) | 122.1 (± 19.51) | | |
| Induction I (n = 105, 90) | 124.8 (± 20.34) | 123.5 (± 20.28) | | |
| Induction II (n = 32, 57) | 121.0 (± 25.09) | 119.8 (± 18.15) | | |
| Consolidation (prior) (n = 210, 196) | 135.9 (± 17.67) | 136.9 (± 21.03) | | |
| Post- consolidation (n = 169, 114) | 143.7 (± 21.45) | 140.1 (± 21.60) | | |
| Follow-up (n = 74, 111) | 136.4 (± 22.87) | 139.2 (± 25.00) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS))

| | |
|-----------------|--|
| End point title | Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS)) |
|-----------------|--|

End point description:

The EQ5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The patient is asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also included a Visual Analogue Scale (VAS), where the patient is asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

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

End point timeframe:

From date of Randomization up to approx. 18 months

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|--------------------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 225, 220) | 62.7 (± 22.98) | 64.3 (± 22.15) | | |
| Induction Phase (n = 135, 146) | 67.9 (± 20.95) | 64.4 (± 21.29) | | |
| Induction I (n = 104, 89) | 68.1 (± 21.02) | 64.0 (± 21.92) | | |
| Induction II (n = 31, 57) | 66.9 (± 21.03) | 65.2 (± 20.44) | | |
| Consolidation (prior) (n = 207, 197) | 79.1 (± 15.42) | 76.2 (± 16.37) | | |
| Post-consolidation (n = 167, 113) | 83.9 (± 15.00) | 77.3 (± 14.92) | | |
| Follow-up (n- 74, 112) | 74.3 (± 20.08) | 73.4 (± 19.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: All Collected Deaths

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

End point description:

On-treatment deaths were collected from start of treatment (FPFT) up to 30 days after study drug discontinuation, for a maximum duration of approx. 18 months.

Deaths post-treatment survival follow up were collected after the on-treatment period up to approx. 18 months. Participants who did not die during the on-treatment period and had not stopped study participation at the time of data cut-off (when study was terminated) were censored.

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

End point timeframe:

Start of study treatment up to 30 days post-treatment for approx. 1 year, prior to study treatment up to LPLV, approx. 18 months

| End point values | Midostaurin + chemotherapy | Placebo + chemotherapy | | |
|-----------------------------|----------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 250 | 251 | | |
| Units: Participants | | | | |
| Total Deaths | 46 | 53 | | |
| Deaths on-treatment | 25 | 21 | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from first dose of study treatment until end of treatment plus 30 days, up to a maximum duration of 573 days for midostaurin and up to a maximum duration of 416 days for Placebo

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 | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|-------------|
| Reporting group title | Midostaurin |
|-----------------------|-------------|

Reporting group description:

Midostaurin

| Serious adverse events | Placebo | Midostaurin | |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 114 / 249 (45.78%) | 95 / 245 (38.78%) | |
| number of deaths (all causes) | 53 | 46 | |
| number of deaths resulting from adverse events | 4 | 6 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Transitional cell carcinoma recurrent | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chloroma | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Embolism | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 4 / 249 (1.61%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 4 | 2 / 2 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 249 (1.61%) | 4 / 245 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Acute graft versus host disease | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Graft versus host disease in gastrointestinal tract | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 6 / 249 (2.41%) | 4 / 245 (1.63%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase | | | |

| | | | |
|--|-----------------|-----------------|--|
| increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocyte count increased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 3 / 249 (1.20%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Expired product administered | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 249 (1.20%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelopathy | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial spasm | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aplastic anaemia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 23 / 249 (9.24%) | 16 / 245 (6.53%) | |
| occurrences causally related to treatment / all | 12 / 32 | 10 / 24 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 249 (0.80%) | 3 / 245 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Jejunal stenosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Mechanical ileus | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |
| subjects affected / exposed | 3 / 249 (1.20%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Oral dysaesthesia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative duodenitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary fistula | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 249 (1.20%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity vasculitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Thyrotoxic crisis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytarabine syndrome | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acinetobacter infection | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspergillus infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary tract infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candida infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral fungal infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridial sepsis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronavirus infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus colitis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 249 (0.80%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatosplenic candidiasis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 3 / 245 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 2 / 245 (0.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 12 / 249 (4.82%) | 9 / 245 (3.67%) | |
| occurrences causally related to treatment / all | 3 / 12 | 6 / 9 | |
| deaths causally related to treatment / all | 2 / 3 | 1 / 1 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 11 / 245 (4.49%) | |
| occurrences causally related to treatment / all | 6 / 16 | 4 / 11 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 4 | |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 9 / 249 (3.61%) | 8 / 245 (3.27%) | |
| occurrences causally related to treatment / all | 1 / 9 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 249 (0.00%) | 3 / 245 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic mycosis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral myocarditis | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 249 (0.00%) | 1 / 245 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 249 (0.40%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 2 / 249 (0.80%) | 0 / 245 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Midostaurin | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 245 / 249 (98.39%) | 242 / 245 (98.78%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 27 / 249 (10.84%) | 20 / 245 (8.16%) | |
| occurrences (all) | 32 | 25 | |
| Hypotension | | | |
| subjects affected / exposed | 25 / 249 (10.04%) | 17 / 245 (6.94%) | |
| occurrences (all) | 27 | 20 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 15 / 249 (6.02%) | 17 / 245 (6.94%) | |
| occurrences (all) | 20 | 22 | |
| Chills | | | |
| subjects affected / exposed | 11 / 249 (4.42%) | 16 / 245 (6.53%) | |
| occurrences (all) | 13 | 23 | |
| Fatigue | | | |
| subjects affected / exposed | 26 / 249 (10.44%) | 36 / 245 (14.69%) | |
| occurrences (all) | 32 | 44 | |
| Mucosal inflammation | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 50 / 249 (20.08%) | 47 / 245 (19.18%) | |
| occurrences (all) | 60 | 53 | |
| Oedema | | | |
| subjects affected / exposed | 21 / 249 (8.43%) | 27 / 245 (11.02%) | |
| occurrences (all) | 25 | 46 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 38 / 249 (15.26%) | 44 / 245 (17.96%) | |
| occurrences (all) | 44 | 54 | |
| Pain | | | |
| subjects affected / exposed | 8 / 249 (3.21%) | 15 / 245 (6.12%) | |
| occurrences (all) | 9 | 17 | |
| Pyrexia | | | |
| subjects affected / exposed | 138 / 249 (55.42%) | 146 / 245 (59.59%) | |
| occurrences (all) | 284 | 308 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 37 / 249 (14.86%) | 33 / 245 (13.47%) | |
| occurrences (all) | 46 | 37 | |
| Dyspnoea | | | |
| subjects affected / exposed | 27 / 249 (10.84%) | 28 / 245 (11.43%) | |
| occurrences (all) | 35 | 44 | |
| Epistaxis | | | |
| subjects affected / exposed | 43 / 249 (17.27%) | 44 / 245 (17.96%) | |
| occurrences (all) | 57 | 58 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 22 / 249 (8.84%) | 17 / 245 (6.94%) | |
| occurrences (all) | 25 | 23 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 15 / 249 (6.02%) | 9 / 245 (3.67%) | |
| occurrences (all) | 18 | 12 | |
| Insomnia | | | |
| subjects affected / exposed | 25 / 249 (10.04%) | 16 / 245 (6.53%) | |
| occurrences (all) | 29 | 18 | |
| Investigations | | | |

| | | | |
|--|-------------------|-------------------|--|
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 9 / 245 (3.67%) | |
| occurrences (all) | 16 | 9 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 249 (7.23%) | 24 / 245 (9.80%) | |
| occurrences (all) | 34 | 33 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 29 / 249 (11.65%) | 29 / 245 (11.84%) | |
| occurrences (all) | 42 | 45 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 7 / 249 (2.81%) | 19 / 245 (7.76%) | |
| occurrences (all) | 10 | 23 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 15 / 245 (6.12%) | |
| occurrences (all) | 19 | 19 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 26 / 245 (10.61%) | |
| occurrences (all) | 14 | 32 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 26 / 249 (10.44%) | 17 / 245 (6.94%) | |
| occurrences (all) | 36 | 22 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 20 / 249 (8.03%) | 20 / 245 (8.16%) | |
| occurrences (all) | 41 | 45 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 50 / 249 (20.08%) | 34 / 245 (13.88%) | |
| occurrences (all) | 119 | 65 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 35 / 249 (14.06%) | 25 / 245 (10.20%) | |
| occurrences (all) | 76 | 45 | |
| Weight increased | | | |
| subjects affected / exposed | 24 / 249 (9.64%) | 17 / 245 (6.94%) | |
| occurrences (all) | 37 | 41 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|--|---|--|
| Transfusion reaction subjects affected / exposed occurrences (all) | 11 / 249 (4.42%) 15 | 13 / 245 (5.31%) 16 | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 16 / 249 (6.43%) 17 | 14 / 245 (5.71%) 15 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 23 / 249 (9.24%) 36 64 / 249 (25.70%) 102 | 14 / 245 (5.71%) 15 70 / 245 (28.57%) 93 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Pancytopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) | 96 / 249 (38.55%) 251 116 / 249 (46.59%) 187 13 / 249 (5.22%) 27 69 / 249 (27.71%) 191 31 / 249 (12.45%) 56 53 / 249 (21.29%) 101 | 77 / 245 (31.43%) 166 102 / 245 (41.63%) 185 6 / 245 (2.45%) 17 62 / 245 (25.31%) 167 20 / 245 (8.16%) 35 34 / 245 (13.88%) 63 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 46 / 249 (18.47%) 54 | 41 / 245 (16.73%) 46 | |

| | | | |
|--|---------------------------|---------------------------|--|
| Abdominal pain upper subjects affected / exposed occurrences (all) | 34 / 249 (13.65%) 40 | 24 / 245 (9.80%) 31 | |
| Constipation subjects affected / exposed occurrences (all) | 84 / 249 (33.73%) 118 | 77 / 245 (31.43%) 112 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 142 / 249 (57.03%) 210 | 121 / 245 (49.39%) 185 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 16 / 249 (6.43%) 17 | 16 / 245 (6.53%) 17 | |
| Haemorrhoids subjects affected / exposed occurrences (all) | 18 / 249 (7.23%) 21 | 27 / 245 (11.02%) 32 | |
| Nausea subjects affected / exposed occurrences (all) | 137 / 249 (55.02%) 227 | 141 / 245 (57.55%) 273 | |
| Stomatitis subjects affected / exposed occurrences (all) | 36 / 249 (14.46%) 41 | 39 / 245 (15.92%) 55 | |
| Proctalgia subjects affected / exposed occurrences (all) | 5 / 249 (2.01%) 7 | 13 / 245 (5.31%) 16 | |
| Neutropenic colitis subjects affected / exposed occurrences (all) | 5 / 249 (2.01%) 5 | 13 / 245 (5.31%) 14 | |
| Vomiting subjects affected / exposed occurrences (all) | 63 / 249 (25.30%) 111 | 101 / 245 (41.22%) 188 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 14 / 249 (5.62%) 14 | 11 / 245 (4.49%) 11 | |
| Dry skin | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 249 (3.21%) | 14 / 245 (5.71%) | |
| occurrences (all) | 12 | 14 | |
| Pruritus | | | |
| subjects affected / exposed | 32 / 249 (12.85%) | 28 / 245 (11.43%) | |
| occurrences (all) | 37 | 33 | |
| Petechiae | | | |
| subjects affected / exposed | 21 / 249 (8.43%) | 20 / 245 (8.16%) | |
| occurrences (all) | 25 | 32 | |
| Erythema | | | |
| subjects affected / exposed | 20 / 249 (8.03%) | 20 / 245 (8.16%) | |
| occurrences (all) | 24 | 26 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 21 / 249 (8.43%) | 17 / 245 (6.94%) | |
| occurrences (all) | 23 | 24 | |
| Rash | | | |
| subjects affected / exposed | 87 / 249 (34.94%) | 80 / 245 (32.65%) | |
| occurrences (all) | 118 | 116 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 14 / 249 (5.62%) | 22 / 245 (8.98%) | |
| occurrences (all) | 18 | 25 | |
| Pain in extremity | | | |
| subjects affected / exposed | 15 / 249 (6.02%) | 23 / 245 (9.39%) | |
| occurrences (all) | 19 | 24 | |
| Bone pain | | | |
| subjects affected / exposed | 13 / 249 (5.22%) | 7 / 245 (2.86%) | |
| occurrences (all) | 14 | 8 | |
| Back pain | | | |
| subjects affected / exposed | 32 / 249 (12.85%) | 26 / 245 (10.61%) | |
| occurrences (all) | 42 | 29 | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 16 / 249 (6.43%) | 9 / 245 (3.67%) | |
| occurrences (all) | 18 | 9 | |
| Sepsis | | | |

| | | | |
|------------------------------------|--------------------|-------------------|--|
| subjects affected / exposed | 13 / 249 (5.22%) | 13 / 245 (5.31%) | |
| occurrences (all) | 14 | 16 | |
| Pneumonia | | | |
| subjects affected / exposed | 29 / 249 (11.65%) | 32 / 245 (13.06%) | |
| occurrences (all) | 30 | 34 | |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 249 (1.61%) | 16 / 245 (6.53%) | |
| occurrences (all) | 4 | 19 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 14 / 249 (5.62%) | 11 / 245 (4.49%) | |
| occurrences (all) | 17 | 12 | |
| Decreased appetite | | | |
| subjects affected / exposed | 40 / 249 (16.06%) | 31 / 245 (12.65%) | |
| occurrences (all) | 50 | 39 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 16 / 249 (6.43%) | 18 / 245 (7.35%) | |
| occurrences (all) | 16 | 19 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 24 / 249 (9.64%) | 15 / 245 (6.12%) | |
| occurrences (all) | 33 | 19 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 102 / 249 (40.96%) | 95 / 245 (38.78%) | |
| occurrences (all) | 171 | 153 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 20 / 249 (8.03%) | 16 / 245 (6.53%) | |
| occurrences (all) | 37 | 27 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 18 / 249 (7.23%) | 16 / 245 (6.53%) | |
| occurrences (all) | 23 | 22 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 08 June 2018 | No subject was enrolled into the study at the time of protocol amendment. Subjects who were screened in the CPKC412A2220 trial and confirmed to be FLT3 mutation negative (SR <0.05) could be offered the opportunity to participate in this study, CPKC412E2301, provided they met all the other inclusion criteria. This change was made due to the implementation of Global Data Protection Regulation on 25-May-2018. |

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.

Notes: