



Clinical trial results:

A phase I/II, open-label, dose-escalating study to evaluate the safety, tolerability and pharmacokinetics of twice daily oral midostaurin and to evaluate the preliminary clinical and pharmacodynamic response in pediatric patients with relapsed or refractory leukemia

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2008-006931-11 |
| Trial protocol | FR SE NL IT |
| Global end of trial date | 21 October 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 02 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CPKC412A2114 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00866281 |
| 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, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000780-PIP01-09 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 September 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 October 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to estimate the maximum tolerated dose (MTD) or to identify the recommended dose for expansion (RDE) for two age groups (3 months to 2 years, and 2 years to 18 years) of pediatric subjects with acute myeloid leukemia (AML) or mixed lineage leukemia gene-rearranged acute lymphoblastic leukemia (MLL) based on the rate of dose-limiting toxicity (DLT) of midostaurin administered orally.

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 | 21 September 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | United States: 2 |
| Worldwide total number of subjects | 22 |
| EEA total number of subjects | 20 |

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) | 11 |

| | |
|---------------------------|---|
| Children (2-11 years) | 2 |
| Adolescents (12-17 years) | 9 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 centres in 5 countries.

Pre-assignment

Screening details:

A total of 22 subjects were enrolled in the study.

Period 1

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

Blinding implementation details:

As the study was an open-label study, this section was not applicable.

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1: Midostaurin (30 milligrams/meters ²) |

Arm description:

Subjects received body-weight and body surface area (BSA) stratified dose of midostaurin 30 mg/m² twice daily (bid) through oral route. The total daily dose in 30 mg/m² bid cohort was 60 mg/m².

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

Dosage and administration details:

Midostaurin 25 mg/mL oral solution was administered bid per BSA (m²) and dose was increased until either the MTD was determined or a 60 mg/m² bid dose was reached.

| | |
|------------------|---|
| Arm title | Cohort 2: Midostaurin (60 mg/m ²) |
|------------------|---|

Arm description:

Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m² bid through oral route. The total daily dose in 60 mg/m² bid cohort was 120 mg/m².

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

Dosage and administration details:

Midostaurin 25 mg/mL oral solution was administered bid per BSA (m²) and dose was increased until either the MTD was determined or a 60 mg/m² bid dose was reached.

| Number of subjects in period 1 | Cohort 1: Midostaurin (30 milligrams/meters ²) | Cohort 2: Midostaurin (60 mg/m ²) |
|--------------------------------|--|---|
| | | |
| Started | 7 | 15 |
| Completed | 0 | 0 |
| Not completed | 7 | 15 |
| Consent withdrawn by subject | 3 | - |
| Disease progression | 3 | 11 |
| Adverse event, non-fatal | 1 | - |
| New cancer therapy | - | 4 |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: Midostaurin (30 milligrams/meters ²) |
| Reporting group description: Subjects received body-weight and body surface area (BSA) stratified dose of midostaurin 30 mg/m ² twice daily (bid) through oral route. The total daily dose in 30 mg/m ² bid cohort was 60 mg/m ² . | |
| Reporting group title | Cohort 2: Midostaurin (60 mg/m ²) |
| Reporting group description: Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m ² bid through oral route. The total daily dose in 60 mg/m ² bid cohort was 120 mg/m ² . | |

| Reporting group values | Cohort 1: Midostaurin (30 milligrams/meters ²) | Cohort 2: Midostaurin (60 mg/m ²) | Total |
|--|--|---|-------|
| Number of subjects | 7 | 15 | 22 |
| Age categorical Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 2 | 9 | 11 |
| Children (2-11 years) | 1 | 1 | 2 |
| Adolescents (12-17 years) | 4 | 5 | 9 |
| Age continuous Units: years | | | |
| arithmetic mean | 9.65 | 6.5 | |
| standard deviation | ± 7.479 | ± 6.903 | - |
| Gender categorical Units: Subjects | | | |
| Female | 5 | 10 | 15 |
| Male | 2 | 5 | 7 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Cohort 1: Midostaurin (30 milligrams/meters ²) |
| Reporting group description: Subjects received body-weight and body surface area (BSA) stratified dose of midostaurin 30 mg/m ² twice daily (bid) through oral route. The total daily dose in 30 mg/m ² bid cohort was 60 mg/m ² . | |
| Reporting group title | Cohort 2: Midostaurin (60 mg/m ²) |
| Reporting group description: Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m ² bid through oral route. The total daily dose in 60 mg/m ² bid cohort was 120 mg/m ² . | |
| Subject analysis set title | AML subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subjects with acute myeloid leukemia (AML) and received body-weight stratified dosage midostaurin 30 or 60 mg/m ² . | |
| Subject analysis set title | MLLr-ALL subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subjects with mixed lineage leukemia gene- rearranged acute lymphoblastic leukemia (MLLr-ALL) and received body-weight stratified dosage midostaurin 30 or 60 mg/m ² . | |

Primary: Maximum tolerated dose (MTD) of midostaurin- Posterior probability of DLT

| | |
|---|--|
| End point title | Maximum tolerated dose (MTD) of midostaurin- Posterior probability of DLT ^[1] |
| End point description: MTD was defined as highest dose level for which no more than 1 subject in a dose cohort experienced dose limiting toxicity(DLT), based on a Bayesian logistic regression model (BLRM) employing the escalation with overdose control(EWOC) principle. A DLT was defined as a grade 3 or 4 non-hematological adverse event(AE) or abnormal laboratory value related to study drug. MTD was not achieved since no more than 1 DLT was observed in any cohort. At the 60mg/m ² dose level, 1 DLT was observed in younger stratum, thus, midostaurin 60 mg/m ² was selected as recommended dose for dose escalation phase. Mean and the 95% posterior probability estimates of having a DLT by age strata and dose is presented. Estimation of MTD and/or RDE at the dose-escalation phase of the study was based upon the estimation of the probability of DLT for subjects in the dose-determining set (DDS). The analysis done in dose-determining set(DDS) population. 'n' signifies the number of evaluable subjects for this measure. | |
| End point type | Primary |
| End point timeframe: Baseline, End of dose escalation phase | |

Notes:

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

Justification: Only descriptive summary statistics was planned for this primary outcome measure.

| End point values | Cohort 1: Midostaurin (30 milligrams/met ers ²) | Cohort 2: Midostaurin (60 mg/m ²) | | |
|--|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 11 | | |
| Units: probability estimates | | | | |
| arithmetic mean (inter-quartile range (Q1-Q3)) | | | | |

| | | | | |
|---|------------------|---------------------|--|--|
| Younger stratum (≥ 3 months - ≤ 2 years): (n=2, 5) | 0.03 (0 to 0.16) | 0.1 (0.01 to 0.33) | | |
| Older stratum (>2 years - <18 years): (n=4, 6) | 0.03 (0 to 0.13) | 0.08 (0.01 to 0.26) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with best overall response by indication

| | |
|-----------------|---|
| End point title | Percentage of subjects with best overall response by indication |
|-----------------|---|

End point description:

The best overall clinical response was determined as per the clinical assessment done by the investigator. Responders were defined as all subjects with a best clinical response of leukemia free state, morphological complete remission, incomplete morphological complete remission, partial remission, bone marrow blast response, bone marrow minor blast response, peripheral blood blast response, minor peripheral blood blast response. Subjects with stable disease, progressive disease and with missing tumour assessment or who discontinued the study or who died before having their first assessment were considered as non-responders. The analysis was performed in full analysis set (FAS) population, defined as all subjects to whom study treatment was assigned.

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

End point timeframe:

Baseline, Day 15 (Day 1 of Cycle 2), Day 22 (Day 8 of Cycle 2), Day 29 (Day 1 of Cycle 9), End of treatment

| End point values | AML subjects | MLLr-ALL subjects | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 9 | 13 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Leukemia free state | 0 | 0 | | |
| Morphological complete remission | 0 | 0 | | |
| Incomplete morphological complete remission | 11.1 | 0 | | |
| Partial remission | 0 | 0 | | |
| Bone marrow blast response | 22.2 | 0 | | |
| Bone marrow minor blast response | 0 | 0 | | |
| Peripheral blood blast response | 11.1 | 23.1 | | |
| Minor peripheral blood blast response | 11.1 | 0 | | |
| Stable disease | 44.4 | 7.7 | | |
| Progressive disease | 0 | 61.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response with midostaurin

| | |
|-----------------|-----------------------------------|
| End point title | Time to response with midostaurin |
|-----------------|-----------------------------------|

End point description:

Time to response was defined as the time from the date of start of midostaurin treatment to the date of first response. Time to response was calculated by using the formula = (date of first response - date of start of midostaurin) + 1 day. Here, "Number of subjects analysed" signifies number of responders at specified time points for each arm, respectively. The analysis was performed in FAS population.

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

End point timeframe:

Baseline, End of treatment

| End point values | AML subjects | MLLr-ALL subjects | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 5 | 3 | | |
| Units: Days | | | | |
| median (full range (min-max)) | 14 (8 to 22) | 8 (3 to 8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival with midostaurin

| | |
|-----------------|-----------------------------------|
| End point title | Overall survival with midostaurin |
|-----------------|-----------------------------------|

End point description:

Overall survival (OS) was defined as the time from start of treatment to date of death due to any cause. The percentage (%) event-free probability estimates were obtained from the Kaplan-Meier survival estimates. The analysis was performed in FAS population.

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

End point timeframe:

Baseline, end of treatment

| End point values | AML subjects | MLLr-ALL subjects | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 9 | 13 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 3.68 (2.727 to 8.312) | 1.35 (0.953 to 2.924) | | |

Statistical analyses

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

| | |
|-----------------|--|
| End point title | Plasma concentrations of midostaurin and its metabolites CGP52421 and CGP62221 |
|-----------------|--|

End point description:

The plasma concentrations of midostaurin (PKC412) and its two major metabolites, CGP62221 and CGP52421 were determined by using a validated liquid chromatography/tandem mass spectrometry method. The analysis was performed in pharmacokinetic (PK) set population defined as all safety set subjects who had at least one valid(measurable) PK sample of midostaurin, and who had no significant restricted co-medications.

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

End point timeframe:

Day 1, Day 5, Day 7, Day 15 (Day 1 of Cycle 2), Day 29 (Day 1 of Cycle 3)

| End point values | Cohort 1: Midostaurin (30 milligrams/met ers^2) | Cohort 2: Midostaurin (60 mg/m^2) | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: nanograms/millilitres (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| PKC412-Cycle 1/Day 1 (1 hour) | 1678 (± 652.817) | 2330.88 (± 1290.136) | | |
| PKC412-Cycle 1/Day 1 (2 hour) | 1762.5 (± 226.771) | 2449.09 (± 936.039) | | |
| PKC412-Cycle 1/Day 1 (3 hour) | 1891.67 (± 505.941) | 2287.5 (± 1421.365) | | |
| PKC412-Cycle 1/Day 1 (12 hour) | 939.17 (± 347.925) | 2068.85 (± 2183.946) | | |
| PKC412-Cycle 1/Day 5 (0 hour) | 2444 (± 936.659) | 2610.1 (± 2480.716) | | |
| PKC412-Cycle 1/Day 7 (0 hour) | 1945 (± 643.467) | 2028 (± 2071.949) | | |
| PKC412-Cycle 2/Day 1 (0 hour) | 1832.5 (± 773.881) | 726 (± 379.953) | | |
| PKC412-Cycle 3/Day 1 (0 hour) | 962 (± 505.146) | 674 (± 340.776) | | |
| CGP62221-Cycle 1/Day 1 (1 hour) | 106.18 (± 89.473) | 228.33 (± 148.469) | | |
| CGP62221-Cycle 1/Day 1 (2 hour) | 208.95 (± 183.22) | 458.75 (± 281.882) | | |
| CGP62221-Cycle 1/Day 1 (3 hour) | 333.4 (± 227.863) | 563.63 (± 276.938) | | |
| CGP62221-Cycle 1/Day 1 (12 hour) | 424.35 (± 299.416) | 730.31 (± 385.698) | | |
| CGP62221-Cycle 1/Day 5 (0 hour) | 3182 (± 1756.778) | 3360.3 (± 2002.498) | | |
| CGP62221-Cycle 1/Day 7 (0 hour) | 3390 (± 1400.071) | 2895 (± 1893.347) | | |
| CGP62221-Cycle 2/Day 1 (0 hour) | 2380 (± 728.331) | 1614.14 (± 1057.585) | | |

| | | | | |
|----------------------------------|---------------------|--------------------|--|--|
| CGP62221-Cycle 3/Day 1 (0 hour) | 1140.67 (± 189.16) | 1759.2 (± 923.668) | | |
| CGP52421-Cycle 1/Day 1 (1 hour) | 71.64 (± 42.325) | 111.58 (± 78.187) | | |
| CGP52421-Cycle 1/Day 1 (2 hour) | 113.23 (± 54.831) | 189.65 (± 128.879) | | |
| CGP52421-Cycle 1/Day 1 (3 hour) | 152.18 (± 78.405) | 236.19 (± 144.723) | | |
| CGP52421-Cycle 1/Day 1 (12 hour) | 139.27 (± 68.198) | 259.52 (± 148.943) | | |
| CGP52421-Cycle 1/Day 5 (0 hour) | 1018 (± 259.014) | 1581 (± 509.208) | | |
| CGP52421-Cycle 1/Day 7 (0 hour) | 1269 (± 453.963) | 2129 (± 341.97) | | |
| CGP52421-Cycle 2/Day 1 (0 hour) | 2350 (± 1110.465) | 2640 (± 541.018) | | |
| CGP52421-Cycle 3/Day 1 (0 hour) | 2386.67 (± 277.909) | 3488 (± 1511.529) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), treatment related AEs or SAEs and death during the study

| | |
|-----------------|---|
| End point title | Number of subjects with adverse events (AEs), serious adverse events (SAEs), treatment related AEs or SAEs and death during the study |
|-----------------|---|

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Treatment related AEs or SAEs were defined as AEs or SAEs that were suspected to be related to study treatment as per investigator. On treatment death was a fatal event leading to permanent cessations of all vital functions of the body. The analysis was performed in safety set population, defined as the subjects who received at least one dose of midostaurin.

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

End point timeframe:

Baseline (start of study treatment) up to End of treatment

| End point values | Cohort 1: Midostaurin (30 milligrams/meters ²) | Cohort 2: Midostaurin (60 mg/m ²) | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 7 | 15 | | |
| Units: Number of subjects | | | | |
| AEs | 6 | 15 | | |
| AEs suspected to be drug related | 1 | 2 | | |
| On-treatment deaths | 2 | 3 | | |

| | | | | |
|-----------------------------------|---|---|--|--|
| SAEs | 3 | 6 | | |
| SAEs suspected to be drug related | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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 | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Cohort 2: Midostaurin (60 mg/m ²) |
|-----------------------|---|

Reporting group description:

Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m² bid through oral route. The total daily dose in 60 mg/m² bid cohort was 120 mg/m².

| | |
|-----------------------|--|
| Reporting group title | Cohort 1: Midostaurin (30 milligrams/meters ²) |
|-----------------------|--|

Reporting group description:

Subjects received BSA stratified dose of midostaurin 30 mg/m² bid through oral route. The total daily dose in 30 mg/m² bid cohort was 60 mg/m².

| Serious adverse events | Cohort 2: Midostaurin (60 mg/m ²) | Cohort 1: Midostaurin (30 milligrams/meters ²) | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 15 (40.00%) | 3 / 7 (42.86%) | |
| number of deaths (all causes) | 3 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blast Cell Count Increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------|----------------|--|
| Tongue Injury | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Cytokine Release Syndrome | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tongue Oedema | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (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 | | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Cohort 2: Midostaurin (60 mg/m²) | Cohort 1: Midostaurin (30 milligrams/meters²) | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 15 (100.00%) | 6 / 7 (85.71%) | |
| Vascular disorders | | | |
| Hyperaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Capillary Leak Syndrome | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Generalised Oedema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Feeling Abnormal | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Crying | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheter Site Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheter Site Inflammation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|--|----------------------|---------------------|--|
| Non-Cardiac Chest Pain subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 7 / 15 (46.67%) 9 | 1 / 7 (14.29%) 1 | |
| Pain subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 0 / 7 (0.00%) 0 | |
| Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Reproductive system and breast disorders Breast Haematoma subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 15 (20.00%) 5 | 0 / 7 (0.00%) 0 | |
| Bronchospasm subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Epistaxis subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 0 / 7 (0.00%) 0 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 3 | 0 / 7 (0.00%) 0 | |
| Hypoxia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Lung Disorder subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |

| | | | |
|-----------------------------|-----------------|---------------|--|
| Rhinalgia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal Congestion | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rales | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung Infiltration | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Mood Altered | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Depression | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Agitation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nightmare | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 4 | 2 | |
| Blood Lactate Dehydrogenase Increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood Albumin Decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood Alkaline Phosphatase Increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood Fibrinogen Decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 5 | 1 | |
| Blood Phosphorus Decreased | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cardiac Murmur | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Electrocardiogram Qt Prolonged | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 3 | 0 / 7 (0.00%) 0 | |
| Haemoglobin Decreased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Heart Sounds Abnormal subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Lipase Increased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Weight Decreased subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 2 | 0 / 7 (0.00%) 0 | |
| Weight Increased subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 3 | 0 / 7 (0.00%) 0 | |
| White Blood Cell Count Decreased subjects affected / exposed occurrences (all) | 2 / 15 (13.33%) 3 | 0 / 7 (0.00%) 0 | |
| White Blood Cell Count Increased subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Injury, poisoning and procedural complications | | | |
| Allergic Transfusion Reaction subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Lower Limb Fracture subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 7 (0.00%) 0 | |
| Cardiac disorders | | | |
| Sinus Tachycardia subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Tachycardia | | | |

| | | | |
|--|---------------------|--------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 2 | 0 / 7 (0.00%) 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 15 (33.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 14 | 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 9 / 15 (60.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 15 (40.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 11 | 1 | |
| Constipation | | | |

| | | | |
|-----------------------------|------------------|----------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal Distension | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mouth Haemorrhage | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Oral Pruritus | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral Pain | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral Mucosal Exfoliation | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 7 / 15 (46.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Tongue Discolouration | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth Loss | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 12 / 15 (80.00%) | 3 / 7 (42.86%) | |
| occurrences (all) | 40 | 4 | |
| Hepatobiliary disorders | | | |

| | | | |
|--|-----------------|----------------|--|
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 1 | |
| Hepatosplenomegaly | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Rash Erythematous | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash Papular | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin Disorder | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Swelling Face | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin Lesion | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain In Jaw | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain In Extremity | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bone Pain | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Enterobacter Sepsis | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Enterobacter Infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Bronchopulmonary Aspergillosis | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Febrile Infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Fungal Infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Viral Infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary Tract Infection | | | |

| | | | |
|------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Staphylococcal Infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung Infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Herpes Zoster | | | |
| subjects affected / exposed | 0 / 15 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 8 | 1 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|-----------------------------|-----------------|----------------|--|
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Decreased Appetite | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 3 | 1 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fluid Retention | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 15 (26.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 9 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 10 November 2009 | 1. The exclusion criteria was modified to allow intrathecal chemotherapy and short courses of corticosteroids as per standard practice for pediatric leukemia. 2.The pharmacokinetic (PK) objective was clarified to evaluate population PK, a term that included peak, trough, and profile. 3.The response criteria were modified in order to provide a definition for treatment failure based on peripheral blood criteria. |
| 11 October 2010 | The instructions for midostaurin administration were modified. |
| 02 April 2013 | 1.The exclusion criteria were modified to allow the subjects who previously treated with sorafenib. 2. The primary objective was modified such way that the milestone of MTD was supplemented with that for RDE, as the dose escalation was constrained to the highest dose of oral midostaurin administered in children, which did not exceed the equivalent adult dose of 100 mg bid. 3.The biomarkers objectives were changed from secondary to exploratory to more accurately reflect the intent of these assessments to generate future hypotheses. |

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.

The study was terminated early since despite considerable efforts to boost recruitment, no new subjects were enrolled in the final year of this study.

Notes: