# Clinical trial results:
# A single arm, Phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukemia +/- an associated hematological clonal non-mast cell lineage disease

## Summary

| | |
|---|---|
| EudraCT number | 2008-000280-42 |
| Trial protocol | BE FR IT DE NO AT GB NL |
| Global end of trial date | 24 August 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 September 2018 |
| First version publication date | 07 September 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CPKC412D2201 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00782067 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 24 August 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to determine the efficacy of midostaurin when administered orally at a dose of 100 mg twice daily (bid) continuously for 6 cycles (of 4 weeks each) in patients with ASM or MCL with or without AHNMD as measured by overall response rate (ORR). The ORR was defined as the percentage of patients classified as confirmed responders (major response [MR] or partial response [PR]) adjudicated by the Study Steering Committee (SSC) according to response assessment criteria specified in the protocol.
Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

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 | 13 October 2008 |
| 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 | Australia: 5 |
| Country: Number of subjects enrolled | Austria: 2 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Germany: 33 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Netherlands: 10 |
| Country: Number of subjects enrolled | Norway: 2 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Turkey: 3 |
| Country: Number of subjects enrolled | United States: 32 |
| Worldwide total number of subjects | 116 |
| EEA total number of subjects | 71 |

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) | 65 |
| From 65 to 84 years | 51 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 29 centers in 12 countries worldwide (Australia, Austria, Belgium, Canada, France, Germany, Netherlands, Norway, Poland, Turkey, United Kingdom, United States).

### Pre-assignment

Screening details:

The Participant Flow was on the Full Analysis Set (FAS), the Baseline Characteristics were done on the FAS and Primary Efficacy Population (PEP). The Efficacy analysis was done on the PEP (except for the Overall Survival which was done on FAS and PEP). The Safety analysis was done on the Safety Set (SS).

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Midostaurin (PKC412) |

Arm description:

Midostaurin was administered at a dose of 100 mg twice daily (bid) in continuous cycles of 28 days until disease progression, intolerable toxicity or withdrawal due to any cause, whichever occurred first.

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

Dosage and administration details:

Midostaurin was administered at a dose of 100 mg twice daily (bid) in continuous cycles of 28 days until disease progression, intolerable toxicity or withdrawal due to any cause, whichever occurred first.

| **Number of subjects in period 1** | Midostaurin (PKC412) |
|---|---|
| Started | 116 |
| Safety Set (SS) | 116 |
| Primary Efficacy Population (PEP) | 89 |
| Completed | 0 |
| Not completed | 116 |
| Adverse event, serious fatal | 9 |
| Subject withdrew consent | 11 |
| Disease progression | 43 |
| Adverse event, non-fatal | 35 |
| Protocol deviation | 2 |
| Administrative problems | 14 |
| Lost to follow-up | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Study |
|---|---|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---|---|---|
| Number of subjects | 116 | 116 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 65 | 65 | |
| From 65-84 years | 51 | 51 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 61.8 | | |
| standard deviation | ± 11.76 | - | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 40 | 40 | |
| Male | 76 | 76 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 2 | |
| White | 111 | 111 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 3 | 3 | |

### Subject analysis sets

| Subject analysis set title | Primary Efficacy Population (PEP) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PEP consisted of patients in the FAS who met the diagnostic criteria for ASM or MCL, and presented with at least one measurable C-finding at study entry and/or patients with transfusion dependent anemia due to their underlying disease at study entry as confirmed by the SSC.

| Subject analysis set title | Full Analysis Set (FAS) |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The FAS was defined according to the Intention to Treat (ITT) principle and comprised all patients to whom study treatment had been assigned. For this single arm study, treatment was considered to be assigned if the patient received at least one dose of the study drug.

| **Reporting group values** | Primary Efficacy Population (PEP) | Full Analysis Set (FAS) | |
|---|---|---|---|
| Number of subjects | 89 | 116 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 63.0 | 61.8 | |
| standard deviation | ± 11.59 | ± 11.76 | |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 32 | 40 | |
| Male | 57 | 76 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 1 | 2 | |
| White | 86 | 111 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 2 | 3 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Midostaurin (PKC412) |

Reporting group description:

Midostaurin was administered at a dose of 100 mg twice daily (bid) in continuous cycles of 28 days until disease progression, intolerable toxicity or withdrawal due to any cause, whichever occurred first.

| | |
|---|---|
| Subject analysis set title | Primary Efficacy Population (PEP) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PEP consisted of patients in the FAS who met the diagnostic criteria for ASM or MCL, and presented with at least one measurable C-finding at study entry and/or patients with transfusion dependent anemia due to their underlying disease at study entry as confirmed by the SSC.

| | |
|---|---|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The FAS was defined according to the Intention to Treat (ITT) principle and comprised all patients to whom study treatment had been assigned. For this single arm study, treatment was considered to be assigned if the patient received at least one dose of the study drug.

### Primary: Percentage of Participants with Overall Response Rate (ORR)

| | |
|---|---|
| End point title | Percentage of Participants with Overall Response Rate (ORR)[1] |

End point description:

Overall Response Rate (ORR) was defined as the percentage of participants who classified as confirmed responders (Major Response (MR) or Partial Response (PR)) by the adjudication of the SSC and based on a Modified Valent Criteria. A major responder had complete resolution of at least one C-Finding and no progression in other C-Findings. A partial responder showed a measurable improvement in one or more C-Finding(s) without confirmed progression in other C-Findings. A C-Finding was a Clinical Finding, which was considered by the investigator and corroborated by the Study Steering Committee (SSC) Chairperson or designee, attributable to the mast cell disease component and not the associated hematological clonal non-mast cell lineage disease (AHNMD) component or any other cause.

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

End point timeframe:

6 months

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: Single arm study. Exact binomial test 95% confidence interval with P value <0.001. Null hypothesis: ORR <= 30%. Alternative hypothesis: ORR >= 50%

| End point values | Primary Efficacy Population (PEP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 59.6 (48.6 to 69.8) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median Time to Duration of response (DoR)

| End point title | Median Time to Duration of response (DoR) |
|---|---|

End point description:

The Duration of response (DoR) was defined as the time from first onset of confirmed response (MR or PR) to the date of first documented and confirmed progression or death due to ASM/MCL.

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

End point timeframe:

Up 5 years

| End point values | Primary Efficacy Population (PEP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 31.4 (10.8 to 999) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median Time to Response (TTR)

| End point title | Median Time to Response (TTR) |
|---|---|

End point description:

The Time to response (TTR) was defined as the time from start of treatment until the date of onset of confirmed response (MR or PR).

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

End point timeframe:

Up 5 years

| End point values | Primary Efficacy Population (PEP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 53 | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 0.3 (0.1 to 3.7) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median Time to Overall Survival (OS)

| End point title | Median Time to Overall Survival (OS) |
|---|---|

End point description:

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

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

End point timeframe:

Up 5 years

| End point values | Midostaurin (PKC412) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 116 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Primary Efficacy Population (PEP) (n=89)\|<br>Full Analysis Set (FAS) (n=116)\| | 26.8 (17.6 to 34.4)<br>28.7 (20.3 to 38.0) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Median Time to Progression-Free Survival (PFS)

| End point title | Median Time to Progression-Free Survival (PFS) |
|---|---|

End point description:

The Progression-free survival (PFS) is defined as the time from start of treatment to the date of the first documented and confirmed progression or death due to any cause.

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

End point timeframe:

Up 5 years

| End point values | Primary Efficacy Population (PEP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 89 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.0 (10.2 to 24.8) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Long-term safety and tolerability of Midostaurin

| End point title | Long-term safety and tolerability of Midostaurin |
|---|---|

End point description:

Analysis of frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC)

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

End point timeframe:

Up to 30 days after last dose of study treatment

| End point values | Midostaurin (PKC412) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 116 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| AEs by Primary System Organ Class (SOC) (n=116)\| | 100 | | | |
| SAEs by Primary System Organ Class (SOC) (n=88)\| | 75.9 | | | |
| Deaths by Primary System Organ Class (SOC) (n=25)\| | 21.6 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Histopathologic response

| End point title | Histopathologic response |
|---|---|

End point description:

Histopathologic response was summarized to demonstrate the change from baseline in percentage of mast cell infiltrations in the Bone Marrow (BM) and related serum tryptase levels.

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

End point timeframe:

Up 5 years

| End point values | Primary Efficacy Population (PEP) | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 89 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| >50% decrease in mast cell (MC) (n=41)\| | 46.1 | | | |
| >0-<=50% decrease in mast cell (MC) (n=19)\| | 21.3 | | | |
| >50% decrease in serum tryptase (n=52)\| | 58.4 | | | |
| >0-<=50% decrease in serum tryptase (n=25)\| | 28.1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Timeframe for AE | |
| Adverse event reporting additional description: | |
| AE additional description | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

| Reporting groups | |
|---|---|
| Reporting group title | Midostaurin |
| Reporting group description: | |
| Midostaurin | |

| Serious adverse events | Midostaurin | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 88 / 116 (75.86%) | | |
| number of deaths (all causes) | 25 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 5 / 116 (4.31%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haematological malignancy | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma of colon | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung neoplasm malignant | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Refractory cytopenia with unilineage dysplasia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myelofibrosis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour compression | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular disorders | | | | |
| Arterial occlusive disease | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flushing | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemodynamic instability | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Heart valve operation | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disease progression | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| General physical health deterioration | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malaise | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple organ dysfunction syndrome | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Oedema peripheral | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Immune system disorders | | | | |
| Anaphylactic shock | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Reproductive system and breast disorders | | | | |
| Ovarian cyst | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Dyspnoea | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 6 / 116 (5.17%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Orthopnoea | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 5 / 116 (4.31%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachypnoea | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Anxiety | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Insomnia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mental status changes | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| Amylase increased | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bleeding time prolonged | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrocardiogram QT prolonged | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrocardiogram ST segment depression | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Troponin increased | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |

| | | | |
|---|---|---|---|
| Muscle strain | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transfusion related complication | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound dehiscence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |

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|---|---|---|---|
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Extrasystoles | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Heart valve incompetence | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Right ventricular failure | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus tachycardia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ventricular tachycardia | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intracranial aneurysm | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Loss of consciousness | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Memory impairment | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Restless legs syndrome | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Anaemia | | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | | |
| occurrences causally related to treatment / all | 1 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coagulopathy | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cytopenia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Disseminated intravascular coagulation | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Eosinophilia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile neutropenia | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 6 / 116 (5.17%) | | | |
| occurrences causally related to treatment / all | 3 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Granulocytopenia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leukocytosis | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphadenopathy | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mastocytosis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neutropenia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Splenic infarction | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombocytopenia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ear and labyrinth disorders | | | | |
| Ear disorder | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Papilloedema | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinopathy hypertensive | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uveitis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 5 / 116 (4.31%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | | |
| occurrences causally related to treatment / all | 2 / 9 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric ulcer | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric varices haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastritis haemorrhagic | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal disorder | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal toxicity | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal ulcer haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhoids | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal mass | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal varices haemorrhage | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pancreatitis acute | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stomatitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Umbilical hernia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Umbilical hernia, obstructive | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Varices oesophageal | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 5 / 116 (4.31%) | | | |
| occurrences causally related to treatment / all | 3 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatobiliary disorders | | | | |
| Bile duct stenosis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholecystitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholecystitis chronic | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholelithiasis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic cirrhosis | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic failure | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatorenal syndrome | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin and subcutaneous tissue disorders | | | | |
| Angioedema | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rash papular | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Skin ulcer | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Toxic skin eruption | | | | |
| subjects affected / exposed | 3 / 116 (2.59%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal and urinary disorders | | | | |
| Acute kidney injury | | | | |
| subjects affected / exposed | 4 / 116 (3.45%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Calculus urinary | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal failure | | | | |
| subjects affected / exposed | 5 / 116 (4.31%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal impairment | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urethral stenosis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Arthralgia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bone pain | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscle haemorrhage | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal stiffness | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myalgia | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteolysis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteonecrosis of jaw | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteosclerosis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal pain | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Bronchitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Campylobacter colitis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile colitis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia urinary tract infection | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral discitis | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nocardiosis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaria | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences causally related to treatment / all | 1 / 11 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 10 / 116 (8.62%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin bacterial infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urethritis | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 116 (4.31%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 116 (1.72%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 116 (0.86%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Midostaurin | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 115 / 116 (99.14%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 9 | | |
| Haematoma | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 9 | | |
| Hypotension | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 12 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 33 / 116 (28.45%) | | |
| occurrences (all) | 39 | | |
| Chills | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 11 | | |
| Oedema | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 41 / 116 (35.34%) | | |
| occurrences (all) | 50 | | |
| Pain | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 8 | | |
| Pyrexia | | | |
| subjects affected / exposed | 30 / 116 (25.86%) | | |
| occurrences (all) | 37 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 22 / 116 (18.97%) | | |
| occurrences (all) | 26 | | |

| | | | |
|---|---|---|---|
| Dyspnoea | | | |
| subjects affected / exposed | 17 / 116 (14.66%) | | |
| occurrences (all) | 19 | | |
| Epistaxis | | | |
| subjects affected / exposed | 14 / 116 (12.07%) | | |
| occurrences (all) | 19 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 9 / 116 (7.76%) | | |
| occurrences (all) | 10 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 8 | | |
| Depression | | | |
| subjects affected / exposed | 13 / 116 (11.21%) | | |
| occurrences (all) | 14 | | |
| Insomnia | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 12 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 10 | | |
| Amylase increased | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 16 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 9 / 116 (7.76%) | | |
| occurrences (all) | 10 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 9 | | |
| Electrocardiogram QT prolonged | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 116 (10.34%) | | |
| occurrences (all) | 17 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 13 | | |
| Lipase increased | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 27 | | |
| Weight decreased | | | |
| subjects affected / exposed | 10 / 116 (8.62%) | | |
| occurrences (all) | 10 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 9 | | |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 8 | | |
| Dizziness | | | |
| subjects affected / exposed | 16 / 116 (13.79%) | | |
| occurrences (all) | 17 | | |
| Headache | | | |
| subjects affected / exposed | 29 / 116 (25.00%) | | |
| occurrences (all) | 46 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 39 / 116 (33.62%) | | |
| occurrences (all) | 58 | | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 8 | | |
| Neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 116 (14.66%) | | |
| occurrences (all) | 34 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 23 / 116 (19.83%) | | |
| occurrences (all) | 34 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 8 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 34 / 116 (29.31%) | | |
| occurrences (all) | 49 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 10 / 116 (8.62%) | | |
| occurrences (all) | 15 | | |
| Ascites | | | |
| subjects affected / exposed | 9 / 116 (7.76%) | | |
| occurrences (all) | 9 | | |
| Constipation | | | |
| subjects affected / exposed | 29 / 116 (25.00%) | | |
| occurrences (all) | 33 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 62 / 116 (53.45%) | | |
| occurrences (all) | 99 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 7 | | |
| Flatulence | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 7 | | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 94 / 116 (81.03%) | | |
| occurrences (all) | 149 | | |
| Vomiting | | | |
| subjects affected / exposed | 77 / 116 (66.38%) | | |
| occurrences (all) | 224 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 7 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Night sweats | | | |
| subjects affected / exposed | 10 / 116 (8.62%) | | |
| occurrences (all) | 10 | | |
| Pruritus | | | |
| subjects affected / exposed | 24 / 116 (20.69%) | | |
| occurrences (all) | 36 | | |
| Rash | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 8 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 24 / 116 (20.69%) | | |
| occurrences (all) | 27 | | |
| Back pain | | | |
| subjects affected / exposed | 26 / 116 (22.41%) | | |
| occurrences (all) | 31 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 13 / 116 (11.21%) | | |
| occurrences (all) | 17 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 19 / 116 (16.38%) | | |
| occurrences (all) | 24 | | |
| Myalgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 10 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 9 / 116 (7.76%) | | |
| occurrences (all) | 10 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 8 | | |
| Cystitis | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 22 | | |
| Oral herpes | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 6 | | |
| Sinusitis | | | |
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 8 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 12 / 116 (10.34%) | | |
| occurrences (all) | 12 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 14 / 116 (12.07%) | | |
| occurrences (all) | 26 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 20 / 116 (17.24%) | | |
| occurrences (all) | 28 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 11 | | |
| Hypocalcaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 116 (5.17%) | | |
| occurrences (all) | 7 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 11 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 8 / 116 (6.90%) | | |
| occurrences (all) | 12 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 7 / 116 (6.03%) | | |
| occurrences (all) | 7 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 11 / 116 (9.48%) | | |
| occurrences (all) | 14 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 November 2008 | Amendment 1 was issued to include changes to the inclusion and exclusion criteria and, to the schedule of examinations to optimize the capturing of disease evolution, and the sampling scheme to alleviate the burden on patients (BM, imaging, PK sampling etc.), and to the overall language for further refinement and better clarity. |
| 23 November 2010 | Amendment 2 was issued to ensure that only patients with measurable C−findings due to mastocytosis were enrolled into the study. Among the Stage I patients enrolled in the study 36% were considered by the SSC to be ineligible for response assessment. To address these issues, systematic collection of the following information was added: history of weight and blood product transfusions, ongoing transfusions, mediator-related symptoms, and antineoplastic therapies since discontinuation of study drug. Changes were made to the response criteria for patients receiving blood transfusions prior to or during study treatment. A patient enrollment approval process by the SSC chair was implemented. Histopathologic response was added as a secondary objective. The definition of the PEP and additional sub-analyses to observe the impact of these were added. In addition, an extension phase was implemented to provide more information on safety and efficacy of midostaurin, and assessment of cardiac function by echocardiogram or MUGA during the study was implemented to allow more frequent monitoring of cardiac function on treatment (previously, assessment of cardiac function was only required at baseline, and further assessments were at the discretion of the investigator). Finally, the recommendation to use prophylactic anti-emetic medication was strengthened to state that anti-emetic medication should be administered to all patients. The type and dose of anti-emetic medication remained at the discretion of the investigator. |
| 10 December 2010 | Amendment 3 was issued to address the request from the Canadian Health Authorities to add an exclusion criterion of "Patients with heart block of any degree at screening". The protocol was amended for Canada only. |
| 08 February 2012 | Amendment 4 was issued to clarify the follow-up for patients who discontinued study treatment in the absence of disease progression (e.g., due to AE). These patients were to be followed for disease status until the time of disease progression, initiation of another antineoplastic therapy, or end of study, whichever was first. Also, the definition of disease progression was updated to comprise a laboratory abnormality not existing at baseline that occurred during study treatment and was attributed to SM. If this new C-Finding demonstrated a worsening > 20% from the value at baseline and was maintained for at least 28 days, this circumstance was defined as disease progression. |
| 20 August 2012 | Amendment 5 was issued to include language that allowed patients to continue to receive midostaurin in accordance with local regulations. |

| | |
|---|---|
| 27 May 2014 | Amendment 6 was issued to revise the definition of the end of study to allow for an extended collection period of efficacy and safety data for midostaurin in a patient population with ASM or MCL. The end of study definition was revised to occur five years after last patient first treatment, or when all patients had discontinued study treatment, whichever occurred first. This extended period of data collection was reviewed through supplemental annual central adjudication meetings by the SSC. Moreover, patients who continued to benefit from treatment with midostaurin could continue to have access to study treatment. Provision for the use of biomarker samples to support other cytokine evaluations and the assessment of mast cell-associated biomarkers, including somatic cytogenetic and genetic/molecular alterations, was added. The visit evaluation schedule was revised according to the new end-of-study definition, and changes were also made to revise the schedule of examinations after three years of study treatment. Contraceptive requirements were revised to also include oral contraceptives based on the results of Study PKC412A2112, which showed that midostaurin is not a strong CYPA4 inducer. In addition, retrospective collection of the date of diagnosis of SM/ASM/MCL was added to allow comparative assessment of OS data from this study with that from historical data. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

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

Notes: