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 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 Units: Years			
arithmetic mean	61.8		
standard deviation	± 11.76	-	
Sex: Female, Male Units: Subjects			
Female	40	40	
Male	76	76	
Race (NIH/OMB) 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 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 Units: Years			
arithmetic mean	63.0	61.8	
standard deviation	± 11.59	± 11.76	
Sex: Female, Male Units: Subjects			
Female	32	40	
Male	57	76	
Race (NIH/OMB) 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)| Full Analysis Set (FAS) (n=116)|	26.8 (17.6 to 34.4) 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		

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			

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				

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				

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				

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			

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				

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				

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				

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				

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				

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				

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: