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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	CPKC412A2114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00866281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	11

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

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 centres in 5 countries.

Pre-assignment

Screening details:

A total of 22 subjects were enrolled in the study.

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

Subjects received body-weight and body surface area (BSA) stratified dose of midostaurin 30 mg/m^2 twice daily (bid) through oral route. The total daily dose in 30 mg/m^2 bid cohort was 60 mg/m^2.

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

Dosage and administration details:

Midostaurin 25 mg/mL oral solution was administered bid per BSA (m^2) and dose was increased until either the MTD was determined or a 60 mg/m^2 bid dose was reached.

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

Arm description:

Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m^2 bid through oral route. The total daily dose in 60 mg/m^2 bid cohort was 120 mg/m^2.

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

Dosage and administration details:

Midostaurin 25 mg/mL oral solution was administered bid per BSA (m^2) and dose was increased until either the MTD was determined or a 60 mg/m^2 bid dose was reached.

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

Baseline characteristics

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

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

End points

End points reporting groups

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with best overall response by indication

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response with midostaurin

End point title	Time to response with midostaurin

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, End of treatment

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival with midostaurin

End point title	Overall survival with midostaurin

End point description:

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

End point type	Secondary

End point timeframe:

Baseline, end of treatment

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

SAEs	3	6		
SAEs suspected to be drug related	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

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

Reporting group description:

Subjects received body-weight and BSA stratified dose of midostaurin 30 mg/m^2 bid through oral route. The total daily dose in 60 mg/m^2 bid cohort was 120 mg/m^2.

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

Reporting group description:

Subjects received BSA stratified dose of midostaurin 30 mg/m^2 bid through oral route. The total daily dose in 30 mg/m^2 bid cohort was 60 mg/m^2.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: