NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Midostaurin / PKC412

Trial Indication(s)

Non-cancer volunteer subjects with hepatic impairment and volunteer subjects with normal hepatic function.

Protocol Number

CPKC412A2116

Protocol Title

An open-label, parallel group, phase I study to assess the pharmacokinetics and safety of midostaurin in subjects with impaired hepatic function and subjects with normal hepatic function.

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: 7 March 2011 (Actual)
Primary Completion Date: 13 April 2020 (Actual)
Study Completion Date: 9 May 2020 (Actual)

Study Design/Methodology

This was an open-label, parallel group, Phase I study to assess the PK and the safety of midostaurin in subjects with impaired hepatic function and in subjects with normal hepatic function.

The study consisted of a Screening period (Day -14 to Day -2), a Baseline period (Day -1), a treatment period of either eleven days (for Child Pugh A and Child Pugh B subjects and matching healthy volunteers) (Groups 1-3), or five days (for Child Pugh C subjects and matching healthy volunteers) (Groups 4 and 5), and a safety follow-up period of 28 days.

At the Screening visit, eligible subjects were enrolled into the study and were assigned to appropriate hepatic function groups (normal hepatic function, mild, moderate and severe hepatic impairment according to the Child-Pugh classification). Each subject in the control group was matched to at least one completed evaluable subject in the group(s) with hepatic impairment with respect to age (± 10 years), body weight (± 20%), body mass index (BMI) (± 5%), and gender.

Child Pugh A and Child Pugh B subjects and matching healthy volunteers received multiple doses of midostaurin (Groups 1-3), Child Pugh C subjects and matching healthy volunteers received a single dose of midostaurin (Groups 4 and 5).

Centers

7 centers in 6 countries: Germany(2), Bulgaria(1), Belgium(1), Romania(1), United States(1), Lithuania(1)

Objectives:

Objectives:

Primary objective

- To assess the PK of midostaurin in subjects with mild (Child Pugh A), moderate (Child Pugh B), and severe (Child Pugh C) impaired hepatic function relative to healthy controls

Secondary objectives:

- To assess the safety and tolerability of midostaurin in subjects with hepatic impairment and matched healthy volunteers
- To explore the relationship between pharmacokinetics and hepatic function parameters after multiple dosing in Child Pugh A and Child Pugh B subjects (and matching healthy volunteers)

- To assess potential CYP3A4 induction by midostaurin in the hepatic impaired population in Child Pugh A and Child Pugh B subjects (and matching healthy volunteers)
- To determine protein binding (and the free fraction) of midostaurin and its metabolites at baseline and following 3 hours after 7 days of multiple dosing (Groups 1-3) or 3 hours after a single dose (Groups 4-5) in each subject

Test Product (s), Dose(s), and Mode(s) of Administration

Midostaurin/ PKC412 (25 mg) was the investigational drug. No reference therapy was administered. All subjects received the same drug regimen under non-fasting conditions, approximately 30 min after the start of a standard meal. Subjects in Groups1-3 received midostaurin 50 mg twice daily orally (with 240 mL of non-carbonated water), on Days 1, 2, 3, 4, 5, 6 and then midostaurin 50 mg once daily on Day 7. Subjects in Groups 4 and 5 received midostaurin 50 mg once daily orally (with 240 mL of non-carbonated water), on Day 1.

Statistical Methods

Primary analysis:

For Groups 1-3, all analyses were performed separately at Day 1 (on the 12 hours PK profile following the first morning dose of midostaurin) and Day 7 (after repeated doses of midostaurin).The analysis of PK parameters at Day 1 were performed on the first dose PK set. The analysis of PK parameters at Day 7 was performed on the full dose PK set. The analysis of AUCCtrough was also performed on the full dose PK set. For Groups 4-5, analyses were performed on the Single dose PK set.

In order to assess the pharmacokinetics of midostaurin in subjects with mild, moderate, and severely impaired hepatic function relative to healthy controls, the primary variables (Cmax, AUC, CL/F and Vz/F for the relevant days and AUCCtrough (Groups 1-3 only)) of midostaurin and its metabolites were analyzed separately on the log scale by means of an ANOVA, using a linear model including the term of impairment group as fixed effect and the geometric mean ratio of PK parameters between each impairment group and control group and the two-sided 90% confidence interval was derived from the model. Additional factors such as log transformed baseline AAG levels, age, weight and sex were also added.

No adjustment of multiplicity was considered since no hypothesis testing was planned.

Median difference of hepatic impairment group and healthy subjects for Tmax of midostaurin and its metabolites were estimated by Hodges Lehman estimator and its exact 90% confidence interval for Day 1 (using the first dose PK set) and again for Day 7 for Groups 1-3 (using the full dose PK set).

Secondary analysis:

Primary and secondary PK parameters of midostaurin and its metabolites (CGP52421 and CGP62221) were summarized by analyte, impairment group and study day (Day 1 and Day 7 (Groups 1-3 only)).

Concentrations of midostaurin and its metabolites (CGP62221 and CGP52421) were summarized by treatment group and scheduled time point reporting n (number of non-missing values), m (number of non-zero values), mean, SD, CV, geometric mean, CV of geometric mean, median, minimum and maximum.

For midostaurin, CGP62221 and CGP52421, 12 hours (96 hours for Groups 4-5) PK profiles at Day 1 and Day 7 (Groups 1-3 only) were shown as figures individually on a linear and semi-log scale. In addition, summary profiles were shown as figures by hepatic impairment group on a linear and semilog scale. For graphical displays, the mean and SD were used. Similarly, summary profile of pre-dose concentrations (from Day 1 pre-dose of the morning dose up to Day 7 (Group 1-3 only) pre-dose) for midostaurin and its metabolites were presented in figures by hepatic impairment group.

For Groups 1-3 the summary statistics of PK parameters at Day 1 was performed on the first dose PK set. The analysis of PK parameters at Day 7 was performed on the full dose PK set. For AUCCtrough, the full dose PK set was also used. For Groups 4-5 the summary statistics of PK parameters after a single dose administration on Day 1 was performed on the Single dose PK set.

Relationship between PK and hepatic function parameters:

For Groups 1-3 the relationship between the primary PK variables at Day 7 (Cmax, AUC0-tau and AUCCtrough of midostaurin only) and hepatic functions (total bilirubin, INR, and albumin levels) were investigated. A linear regression model predicting log-transformed PK parameter at Day 7 by log-transformed liver function at Day 7 was fitted using the full dose PK set.

The regression coefficients representing the relationship between the PK parameters and the hepatic function parameters were estimated together with its 90% CI from the model.

Figures showed individual’s PK parameters versus each hepatic function values (INR, bilirubin and albumin) using different symbols for the impairment groups separately at Day 1 and Day 7. Regression lines were added as appropriate.

Free fraction concentrations of midostaurin and its metabolites:

Fraction unbound of midostaurin and its metabolites were summarized in descriptive statistics by analyte, treatment group, and study day (Day 1 and Day 7 (Groups 1-3 only)).

Cmax, AUC0-tau and AUCCtrough were expressed in terms of unbound concentrations (by multiplying the PK parameter by the fraction unbound observed on the same day) and were summarized in descriptive statistics by analyte, impairment group and study day similarly as for PK parameters on the total concentrations.

The summary statistics of unbound fraction at Day 1 and Day 7 were performed on the first dose PK set and full dose PK sets respectively for Groups 1-3 and at Day 1 using the Single dose PK set for Groups 4-5.

For Groups 1-3 the primary analyses were repeated for Cmax and AUC0-tau at Day 1 and 7 and AUCCtrough of the parent compound and its metabolites expressed in term of unbound concentration.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- Adult male or female subjects age 18-70 years
- Negative serum beta-hCG pregnancy test for all women prior to starting treatment
- Normal vital signs, body weight, BMI and laboratory test results
- Willing to comply with dietary, fluid and lifestyle restrictions
- Able to communicate well with the Investigator and comply with the requirements of the study.

Additional Inclusion Criteria for hepatic impaired subjects
- Physical signs consistent with hepatic impairment
- CPC score consistent with degree of hepatic impairment
- Serum creatinine <=2xULN
- ANC >1000cells/mm3, hemaglobin >9g/dL, platelet count > 50,000/mm3 (Group 2-3 only)

Key Exclusion Criteria:
- Significant neurologic or psychiatric disorder which could compromise participation in the study.
- History of: seizures requiring anti-convulsant therapy; unstable COPD; GI or rectal bleeding 3 weeks prior to study start; Myocardial Infarction within 12 months; unstable or poorly controlled angina or other clinically significant heart disease; clinically significant urinary obstruction or difficulty voiding; clinically significant ECG abnormalities or long QT-interval syndrome; pancreatic injury or pancreatitis
- Concurrent severe / uncontrolled medical conditions
- Significant illness within 2 weeks prior to dosing or hospitalisation within 4 weeks prior to dosing
- Any surgical or medical condition that may significantly affect absorption, distribution, metabolism or excretion of drugs
- Clinically significant ECG abnormalities at screening
- Cotinine levels greater than 500ng/mL (Group 1-3) or smokers not willing to limit tobacco or nicotine products equivalent to 10 cigarettes per day (Group 4 and 5) for 1 week prior to dosing and throughout hospital confinement
- Consumption of alcohol within 3 days (Group 1-3) or within 2 days (Groups 4 and 5) prior to dosing or during the study.
- Administration of CYP3A4/5 or P-gp inducing or inhibiting drugs within 14 days prior to dosing or during the study
- Sexually active males unless they use condom during intercourse while taking midostaurin and for at least 3 months after the last exposure to drug.
- Use of any prescription drug within 2 weeks or over the counter medication within 72 hours prior to dosing
- Consumption of grapefruit, grapefruit juice, Seville oranges, start fruit / juice within 72 hours prior to dosing

Additional exclusion criteria for healthy controls
- Clinical evidence of liver disease or liver injury
- Positive HBsAg or Hep C test result

Additional exclusion criteria for hepatic impairment subjects
- Symptoms or history of >=G3 hepatic encephalopathy; surgical portosystemic shunt
- PTT >2.5xULN; INR >3; Total bilirubin >6mg/dL
- Evidence of progressive liver disease within 4 weeks prior to starting study
- Clinical evidence of severe >=G3 ascites (Groups 2 and 3)

Participant Flow Table

Overall Study

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5	Total
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	
Started	13	10	7	6	7	43
Completed	12	9	6	6	7	40
Not Completed	1	1	1	0	0	3
Protocol Violation	1	1	1	0	0	3

Baseline Characteristics

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5	Total
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	
Number of Participants [units: participants]	13	10	7	6	7	43
Age, Customized (units: Participants)						
Adults (18 - 64 years)	12	9	5	6	7	39
Elderly (from 65 - 84 years)	1	1	2	0	0	4

Sex: Female, Male
(units: Participants)
Count of Participants (Not Applicable)

Female	4	2	3	4	4	17
Male	9	8	4	2	3	26
Race/Ethnicity, Customized (units: Participants)						
Caucasian	13	10	7	5	7	42
Other	0	0	0	1	0	1

Primary Outcome Result(s)

Peak Plasma Concentrations (Cmax) for midostaurin at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax)			

for midostaurin at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	1206.47 (19.31%)	697.86 (28.08%)	628.91 (55.61%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Method	linear model of the log-transformed PK
Other Geo-mean ratio Comparison	0.58
95 % Confidence Interval 2-Sided	0.46 to 0.73

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.52
95 % Confidence Interval 2-Sided	0.40 to 0.68

Pharmacokinetics (PK) parameter: AUC0-12h for midostaurin at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Pharmacokinetics (PK) parameter: AUC0-12h for midostaurin at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	8132.92 (16.44%)	4941.26 (26.80%)	5227.95 (60.84%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparisons	0.61

95 % Confidence Interval 2-Sided	0.48 to 0.77

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Comparisons	0.64
95 % Confidence Interval 2-Sided	0.49 to 0.84

PK parameter: Tmax for midostaurin at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6

PK parameter: Tmax for midostaurin at Day 1 (units: hr) Median (Full Range)			
	2.99 (1.0 to 4.0)	3.00 (1.0 to 4.0)	6.02 (4.0 to 8.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.02
95 % Confidence Interval 2-Sided	-0.3 to 1.00

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	3.50
95 % Confidence Interval 2-Sided	1.03 to 5.02

Peak Plasma Concentrations (Cmax) for midostaurin at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax) for midostaurin at Day 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	1611.90 (27.92%)	1034.84 (45.00%)	1086.47 (41.58%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Method	linear model of the log-transformed PK

Other Geo-mean ratio Comparison	0.64
95 % Confidence Interval 2-Sided	0.49 to 0.84

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.67
95 % Confidence Interval 2-Sided	0.50 to 0.92

PK parameter: AUC0-tau for midostaurin at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.

Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-tau for midostaurin at Day 7 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	13103.43 (28.97%)	9410.51 (49.27%)	10498.39 (37.51%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparisons	0.72
95 % Confidence Interval 2-Sided	0.54 to 0.95

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparisons	0.80
95 % Confidence Interval 2-Sided	0.58 to 1.10

PK parameter: AUC Ctrough for midostaurin at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for midostaurin at Day 7 (units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	5407.75 (26.02%)	3534.39 (28.78%)	4325.50 (29.83%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2

Other Geo-mean ratio Comparisons	0.65
95 % Confidence Interval 2-Sided	0.53 to 0.81

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparisons	0.80
95 % Confidence Interval 2-Sided	0.59 to 1.09

PK parameter: Tmax for midostaurin at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6

			and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Tmax for midostaurin at Day 7 (units: hr) Median (Full Range)			
	2.00 (1.0 to 3.0)	2.02 (1.0 to 4.0)	2.50 (1.0 to 4.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.98
95 % Confidence Interval 2-Sided	0.00 to 1.02

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.50
95 % Confidence Interval 2-Sided	-0.97 to 1.98

Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP52421 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP52421 at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)	209.29 (20.00%)	138.25 (28.74%)	161.21 (24.42%)

Statistical Analysis

Groups	Normal hepatic function - Group 1,

	Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.66
95 % Confidence Interval 2-Sided	0.55 to 0.79

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.77
95 % Confidence Interval 2-Sided	0.63 to 0.94

PK parameter: AUC0-12h for midostaurin metabolite CGP52421 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-

		6 and 50mg o.d on day 7.	6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for midostaurin metabolite CGP52421 at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	1881.59 (19.81%)	1241.84 (27.41%)	1354.24 (32.90%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.66
95 % Confidence Interval 2-Sided	0.55 to 0.80

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.72

95 % Confidence Interval 2-Sided	0.58 to 0.89

PK parameter: Tmax for midostaurin metabolite CGP52421 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Tmax for midostaurin metabolite CGP52421 at Day 1 (units: hr) Mean (Full Range)			
	4.00 (3.0 to 8.0)	4.02 (4.0 to 8.0)	8.00 (4.0 to 12.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.02
95 % Confidence Interval 2-Sided	0.00 to 1.03

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	4.00
95 % Confidence Interval 2-Sided	0.05 to 5.00

Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP52421 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg

	6 and 50mg o.d on day 7.	50mg b.i.d from days 1-6 and 50mg o.d on day 7.	b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP52421 at Day 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	1176.74 (19.19%)	874.08 (17.49%)	1104.54 (16.87%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.74
95 % Confidence Interval 2-Sided	0.65 to 0.85

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3

Other Geo-mean ratio Comparison	0.94
95 % Confidence Interval 2-Sided	0.80 to 1.10

PK parameter: AUC0-tau for midostaurin metabolite CGP52421 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-tau for midostaurin metabolite CGP52421 at Day 7 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	13152.21 (21.24%)	9573.33 (16.51%)	11855.31 (19.28%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.73
95 % Confidence Interval 2-Sided	0.63 to 0.84

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.90
95 % Confidence Interval 2-Sided	0.76 to 1.06

PK parameter: AUC Ctrough for midostaurin metabolite CGP52421 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were

	b.i.d from days 1-6 and 50mg o.d on day 7.	treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for midostaurin metabolite CGP52421 at Day 7 (units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	3623.77 (20.27%)	2711.23 (16.14%)	3868.37 (16.27%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.75
95 % Confidence Interval 2-Sided	0.65 to 0.86

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3

Other Geo-mean ratio Comparison	1.07
95 % Confidence Interval 2-Sided	0.87 to 1.31

PK parameter: Tmax for midostaurin metabolite CGP52421 dosing at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Tmax for midostaurin metabolite CGP52421 dosing at Day 7 (units: hr) Mean (Full Range)			
	3.00 (2.0 to 4.0)	3.00 (0.0 to 23.8)	4.00 (0.0 to 72.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.97
95 % Confidence Interval 2-Sided	0.00 to 1.00

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	1.52
95 % Confidence Interval 2-Sided	0.97 to 10.00

Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP62221 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with	Subjects with mild hepatic function - Child-Pugh A classification score 5-6.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9.

	midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP62221 at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	531.82 (10.07%)	325.40 (24.38%)	281.29 (52.26%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.61
95 % Confidence Interval 2-Sided	0.50 to 0.75

Statistical Analysis

Groups	Normal hepatic function - Group 1,

	Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.53
95 % Confidence Interval 2-Sided	0.42 to 0.67

PK parameter: AUC0-12h for midostaurin metabolite CGP62221 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for midostaurin metabolite CGP62221 at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			

	4945.85 (13.21%)	2995.03 (26.38%)	2407.16 (59.03%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.61
95 % Confidence Interval 2-Sided	0.48 to 0.76

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	0.49
95 % Confidence Interval 2-Sided	0.38 to 0.63

PK parameter: Tmax for midostaurin metabolite CGP62221 at Day 1

(Time Frame: at different timepoints on Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group	Subjects with mild hepatic function -	Subjects with moderate hepatic

	(Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Tmax for midostaurin metabolite CGP62221 at Day 1 (units: hr) Mean (Full Range)			
	4.00 (4.0 to 8.0)	4.03 (3.0 to 12.0)	10.01 (8.0 to 12.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.02
95 % Confidence Interval 2-Sided	-0.2 to 4.00

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ratio Comparison	4.02
95 % Confidence Interval 2-Sided	3.97 to 7.97

Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP62221 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Peak Plasma Concentrations (Cmax) for midostaurin metabolite CGP62221 at Day 7 (units: ng/mL)			

Geometric Mean (Geometric Coefficient of Variation)			
	1667.94 (24.26%)	1075.90 (36.90%)	1097.80 (47.03%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ration Comparison	0.65
95 % Confidence Interval 2-Sided	0.50 to 0.83

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ration Comparison	0.66
95 % Confidence Interval 2-Sided	0.50 to 0.87

PK parameter: AUC0-tau for midostaurin metabolite CGP62221 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**

Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-tau for midostaurin metabolite CGP62221 at Day 7 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	18384.06 (25.07%)	11423.47 (36.40%)	11736.67 (51.22%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ratio Comparison	0.62
95 % Confidence Interval 2-Sided	0.48 to 0.81

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ration Comparison	0.64
95 % Confidence Interval 2-Sided	0.48 to 0.86

PK parameter: AUC Ctrough for midostaurin metabolite CGP62221 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for midostaurin metabolite CGP62221 at Day 7			

(units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	7930.54 (16.08%)	4704.12 (25.34%)	5280.23 (58.77%)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ration Comparison	0.59
95 % Confidence Interval 2-Sided	0.48 to 0.73

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ration Comparison	0.67
95 % Confidence Interval 2-Sided	0.49 to 0.90

PK parameter: Tmax for midostaurin metabolite CGP62221 at Day 7

(Time Frame: at different timepoints on Day 7)

	Normal hepatic	**Mild hepatic impairment - Group 2**	**Moderate hepatic**

	function - Group 1		impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Tmax for midostaurin metabolite CGP62221 at Day 7 (units: hr) Mean (Full Range)			
	2.50 (0.0 to 8.0)	4.00 (0.0 to 23.8)	1.52 (0.0 to 4.0)

Statistical Analysis

Groups	Normal hepatic function - Group 1, Mild hepatic impairment - Group 2
Other Geo-mean ration Comparison	1.03

95 % Confidence Interval 2-Sided	0.00 to 8.92

Statistical Analysis

Groups	Normal hepatic function - Group 1, Moderate hepatic impairment - Group 3
Other Geo-mean ration Comparison	1.00
95 % Confidence Interval 2-Sided	-0.02 to 2.03

Peak Plasma Concentrations (Cmax) for midostaurin at Day 1 (single dose)

(Time Frame: at different timepoints on Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a

		single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
Peak Plasma Concentrations (Cmax) for midostaurin at Day 1 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	305 (15.8%)	1360 (29.9%)

Statistical Analysis

Groups	Severe hepatic impairment - Group 4, Normal hepatic function - Group 5
Other Geo-mean ratio Comparisons	0.224
95 % Confidence Interval 2-Sided	0.175 to 0.286

PK parameter: AUC0-12h for midostaurin on Day 1 (single dose)

(Time Frame: at different timepoints at Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**

Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: AUC0-12h for midostaurin on Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
	2270 (18.5%)	8460 (21.7%)

Statistical Analysis

Groups	Severe hepatic impairment - Group 4,

	Normal hepatic function - Group 5
Other Geo-mean ratio Comparison	0.269
95 % Confidence Interval 2-Sided	0.218 to 0.331

PK parameter: AUCinf for midostaurin at Day 1 (single dose)

(Time Frame: at different timepoints from on Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	2	6

PK parameter: AUCinf for midostaurin at Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
	12400 (41.9%)	30100 (33.6%)

Statistical Analysis

Groups	Severe hepatic impairment - Group 4, Normal hepatic function - Group 5
Other Geo-mean ratio Comparisons	0.413
95 % Confidence Interval 2-Sided	0.241 to 0.709

PK parameter: AUClast for midostaurin at Day 1 (single dose)

(Time Frame: at different timepoints on Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI

	single dose of midostaurin of 50mg on day 1.	and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: AUClast for midostaurin at Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
	11100 (25.3%)	26600 (29.1%)

Statistical Analysis

Groups	Severe hepatic impairment - Group 4, Normal hepatic function - Group 5
Other Geo-mean ratio Comparisons	0.419
95 % Confidence Interval 2-Sided	0.316 to 0.554

PK parameter: Tmax for midostaurin at Day 1 (single dose)

(Time Frame: at different timepoints on Day 1)

	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: Tmax for midostaurin at Day 1 (single dose) (units: hr) Mean (Full Range)		
	4 (2 to 4)	2.5 (1.5 to 6)

Statistical Analysis

Groups	Severe hepatic impairment - Group 4, Normal hepatic function - Group 5
Other Adjusted Geo-mean ratio Comparisons	1.00
95 % Confidence Interval 2-Sided	-1.00 to 2.50

PK parameter: Tlast for midostaurin at Day 1 (single dose)

(Time Frame: at different timepoints on Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.

Number of Participants Analyzed [units: participants]	6	6
PK parameter: Tlast for midostaurin at Day 1 (single dose) (units: hr) Mean (Full Range)		
	96 (96 to 96)	96 (96 to 96)

Secondary Outcome Result(s)

Potential CYP3A4 induction: 6 Betahydroxycortisol/ cortisol ratio by midostaurin in the hepatic impaired population

(Time Frame: Baseline, Day 3, Day 7 end of study (Day 11))

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.

Number of Participants Analyzed [units: participants]	12	9	6
Potential CYP3A4 induction: 6 Betahydroxycortisol/ cortisol ratio by midostaurin in the hepatic impaired population (units: ratio) Median (Full Range)			
Baseline	4.41 (3.26 to 11.1)	7.22 (3.32 to 13.4)	4.6 (3.43 to 17.3)
Day 3 (n = 12, 8, 6)	5.07 (2.48 to 7.62)	6.45 (3.93 to 26.6)	4.59 (2.56 to 10)
Day 7	6.02 (0 to 9.12)	4.84 (1.78 to 14.1)	4.06 (3.3 to 13.2)
EOS (Day 11)	5.81 (1.93 to 10.1)	6.61 (2.54 to 10.4)	5.17 (2.9 to 16.3)

Pharmacokinetics (PK) Parameter: Cmax for Unbound concentrations of midostaurin at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6

			and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
Pharmacokinetics (PK) Parameter: Cmax for Unbound concentrations of midostaurin at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	7.96 (26.77%)	6.16 (45.77%)	5.72 (72.51%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.

Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	53.68 (24.23%)	43.65 (43.64%)	47.57 (62.93%)

PK parameter: Cmax for Unbound concentrations of midostaurin at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6

PK parameter: Cmax for Unbound concentrations of midostaurin at Day 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	18.47 (51.00%)	12.68 (33.62%)	15.50 (80.19%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin at Day 7 (units: ng.h/mL) Geometric Mean			

(Geometric Coefficient of Variation)			
	150.11 (53.19%)	115.28 (36.47%)	149.80 (82.13%)

PK parameter: AUC Ctrough for Unbound concentrations of midostaurin at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for Unbound concentrations of midostaurin at Day 7 (units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	64.20 (44.66%)	43.30 (41.36%)	95.04 (79.27%)

PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP52421 at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP52421 at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	2.00 (57.69%)	1.59 (38.90%)	2.10 (83.11%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP52421 at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP52421 at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	17.98 (58.15%)	14.24 (38.95%)	17.68 (95.02%)

PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	11.11 (41.79%)	9.97 (31.98%)	18.41 (62.58%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic

			impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	124.22 (42.52%)	109.22 (28.01%)	197.65 (60.07%)

PK parameter: AUC Ctrough for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3

Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for Unbound concentrations of midostaurin metabolite CGP52421 at Day 7 (units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	35.94 (46.65%)	30.93 (24.96%)	76.98 (78.23%)

PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP62221 at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched	Subjects with mild hepatic function -	Subjects with moderate hepatic

	controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP62221 at Day 1 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	2.04 (100.54%)	2.25 (77.72%)	3.65 (39.82%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP62221 at Day 1

(Time Frame: Day 1)

	Normal hepatic function - Group 1	Mild hepatic impairment - Group 2	Moderate hepatic impairment - Group 3
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with	Subjects with mild hepatic function - Child-Pugh A classification score 5-6.	Subjects with moderate hepatic function - Child Pugh B classification

	midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP62221 at Day 1 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	19.00 (103.11%)	20.74 (81.86%)	31.24 (50.19%)

PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with

	from days 1-6 and 50mg o.d on day 7.	50mg b.i.d from days 1-6 and 50mg o.d on day 7.	midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: Cmax for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7 (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)			
	9.87 (64.26%)	7.40 (67.20%)	16.24 (33.46%)

PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and

		and 50mg o.d on day 7.	50mg o.d on day 7.
Number of Participants Analyzed [units: participants]	12	9	6
PK parameter: AUC0-12h for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7 (units: ng.h/mL) Geometric Mean (Geometric Coefficient of Variation)			
	108.83 (64.62%)	78.60 (66.68%)	173.61 (31.99%)

PK parameter: AUC Ctrough for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7

(Time Frame: Day 7)

	Normal hepatic function - Group 1	**Mild hepatic impairment - Group 2**	**Moderate hepatic impairment - Group 3**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.

Number of Participants Analyzed [units: participants]	10	9	3
PK parameter: AUC Ctrough for Unbound concentrations of midostaurin metabolite CGP62221 at Day 7 (units: ng.day/mL) Geometric Mean (Geometric Coefficient of Variation)			
	43.89 (69.52%)	32.37 (53.34%)	87.07 (25.13%)

PK parameter: Cmax of unbound plasma concentrations of midostaurin at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a

		single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: Cmax of unbound plasma concentrations of midostaurin at Day 1 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	3.07 (55%)	7.39 (57.8%)

PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic

	50mg on day 1.	function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin at Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
AUC0-12h	22.9 (56.2%)	45.9 (41.4%)
AUCinf (n = 2, 6)	131 (45.7%)	164 (36.9%)
AUClast	112 (49.6%)	144 (33.9%)

PK parameter: Cmax of unbound plasma concentrations of midostaurin metabolite CGP52421 at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to

	single dose of midostaurin of 50mg on day 1.	subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: Cmax of unbound plasma concentrations of midostaurin metabolite CGP52421 at Day 1 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	1.17 (35.4%)	1.13 (64.7%)

PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin metabolite CGP52421 at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**
Arm/Group Description	Subjects with severe hepatic impairment	Matched control for group 4 - healthy

	function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin metabolite CGP52421 at Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
AUC0-12h	9.95 (38.6%)	8.84 (57.9%)
AUCinf (n = 0, 0)		
AUClast	79.4 (42.6%)	57.1 (61.9%)

PK parameter: Cmax of unbound plasma concentrations of midostaurin metabolite CGP62221 at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	**Normal hepatic function - Group 5**

Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: Cmax of unbound plasma concentrations of midostaurin metabolite CGP62221 at Day 1 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	1.42 (48.2%)	1.99 (40.3%)

PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin metabolite CGP62221 at Day 1 (single dose)

(Time Frame: Day 1)

	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
PK parameter: AUC (AUC0-12h, AUCinf, AUClast) of unbound plasma concentrations of midostaurin metabolite CGP62221 at Day 1 (single dose) (units: ng*h/mL) Geometric Mean (Geometric Coefficient of Variation)		
AUC0-12h	12.7 (52.1%)	16.5 (41.5%)

AUCinf (n = 0, 1)		125 (0%)
AUClast	104 (42.8%)	116 (31.8%)

Free (unbound) fraction of midostaurin (single dose)

(Time Frame: 3 hours post single dose)

	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
Free (unbound) fraction of midostaurin (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	0.0101 (46.8%)	0.00543 (50.9%)

Free (unbound) fraction of midostaurin metabolite CGP52421 (single dose)

(Time Frame: 3 hours post single dose)

	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
Free (unbound) fraction of midostaurin metabolite CGP52421 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	0.0167 (40.4%)	0.00792 (56.1%)

Free (unbound) fraction of midostaurin metabolite CGP62221 (single dose)

(Time Frame: 3 hours post single dose)

	Severe hepatic impairment - Group 4	Normal hepatic function - Group 5
Arm/Group Description	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.
Number of Participants Analyzed [units: participants]	6	6
Free (unbound) fraction of midostaurin metabolite CGP62221 (single dose) (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	0.00839 (41.8%)	0.00345 (55%)

Safety Results

All-Cause Mortality

	Normal hepatic function - Group 1 N = 13	Mild hepatic impairment - Group 2 N = 10	Moderate hepatic impairment - Group 3 N = 7	Severe hepatic impairment - Group 4 N = 7	Normal hepatic function - Group 5 N = 6	All subjects N = 43
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	All subjects enrolled in the study
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	Normal hepatic function - Group 1 N = 13	**Mild hepatic impairment - Group 2 N = 10**	**Moderate hepatic impairment - Group 3 N = 7**	**Severe hepatic impairment - Group 4 N = 7**	**Normal hepatic function - Group 5 N = 6**	**All subjects N = 43**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6 and 50mg o.d on day 7.	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	All subjects enrolled in the study
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.33%)

Gastrointestinal disorders						
Gastric ulcer	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.33%)
Infections and infestations						
Peritonitis bacterial	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.33%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Normal hepatic function - Group 1 N = 13	**Mild hepatic impairment - Group 2 N = 10**	**Moderate hepatic impairment - Group 3 N = 7**	**Severe hepatic impairment - Group 4 N = 7**	**Normal hepatic function - Group 5 N = 6**	**All subjects N = 43**
Arm/Group Description	Normal hepatic function group (Matched controls). Subjects were treated with midostaurin 50mg b.i.d from days 1-6	Subjects with mild hepatic function - Child-Pugh A classification score 5-6. Subjects were treated with midostaurin 50mg b.i.d from days 1-6	Subjects with moderate hepatic function - Child Pugh B classification score 7-9. Subjects were treated with midostaurin 50mg b.i.d from days 1-6	Subjects with severe hepatic impairment function - Child Pugh C classification score 10-15. Subjects were treated with a single dose of midostaurin of	Matched control for group 4 - healthy volunteers matched with respect to age, body weight, BMI and gender to subjects in severe	All subjects enrolled in the study

	and 50mg o.d on day 7.	and 50mg o.d on day 7.	and 50mg o.d on day 7.	50mg on day 1.	hepatic function group. Subjects were treated with a single dose of midostaurin of 50mg on day 1.	
Total participants affected	2 (15.38%)	5 (50.00%)	4 (57.14%)	2 (28.57%)	1 (16.67%)	14 (32.56%)
Gastrointestinal disorders						
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (2.33%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (2.33%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.33%)
Hypoaesthesia oral	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.33%)
Nausea	2 (15.38%)	2 (20.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	5 (11.63%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.33%)
Hepatobiliary disorders						
Hyperbilirubinaemia	0 (0.00%)	2 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.65%)
Infections and infestations						
Urinary tract infection	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.33%)
Investigations						
Alanine aminotransferase increased	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.33%)

Aspartate aminotransferase increased	0 (0.00%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.33%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (2.33%)
Lipase increased	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (2.33%)
Nervous system disorders						
Dizziness	1 (7.69%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.65%)
Headache	1 (7.69%)	1 (10.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.65%)
Skin and subcutaneous tissue disorders						
Rash	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (2.33%)

Conclusion:

- There was no increase in exposure to plasma midostaurin and metabolites (CGP52421 or CGP62221) in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) ~~hepatic impairment~~ or severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function during the study. In contrast, a decrease was observed.
- There was a decrease in exposure (Cmax and AUCs) to plasma unbound midostaurin in subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function.
- A decrease was generally observed in the exposure (Cmax and AUCs) for the unbound metabolite CGP62221 in the subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function.
- The Cmax and AUC0-12h of unbound CGP52421 were similar for both control and the severe hepatic impairment group and AUClast slightly increased in subjects with severe hepatic impairment compared to subjects with normal hepatic function.
- No CYP3A4 induction was detected in mild and moderate hepatic impairment groups following 7 days of treatment.
- The administration of multiple oral doses of midostaurin 50 mg twice daily for 6 days was well tolerated in subjects with normal hepatic function, with mild hepatic impairment and with moderate hepatic impairment, and there were no new or changing safety signals.
- The administration of a single oral dose of midostaurin 50 mg was well tolerated in subjects with normal hepatic function and with severe hepatic impairment, and there were no new or changing safety signals.

Date of Clinical Trial Report

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