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Sponsor

Novartis

Generic Drug Name

Capmatinib

Trial Indication(s)

Impaired Hepatic Function

Protocol Number

CINC280A2106

Protocol Title

An open label, single-dose, multi-center, parallel-group, two-staged study to evaluate the pharmacokinetics of the oral cMET inhibitor INC280 in non-cancer subjects with impaired hepatic function and non-cancer subjects with normal hepatic function

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

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Study Start/End Dates

12-Jun-2015 to 12-Sep-2017

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Phase I, multi-center, open-label, single oral dose, parallel group study to evaluate the pharmacokinetics of capmatinib in non-cancer subjects with impaired hepatic function and non-cancer subjects with normal hepatic function. This study consisted the following periods:

- Screening/Baseline period: Baseline evaluations were performed within 21 days prior to capmatinib dosing
- Treatment/Observation period: Subjects were confined and received a single oral dose of 200 mg capmatinib (2 × 100 mg tablets) on Day 1
- End of Treatment (EOT): On Day 4, subjects underwent end of treatment evaluations and were discharged
- End of Study (EOS): Subjects were contacted by phone for safety follow-up 30 days after dosing to collect and record adverse events (AEs) and serious adverse events (SAEs) that might have occurred following the dose administration and/or follow resolution of ongoing AEs, if applicable.

In Stage 1, subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment were enrolled. Enrollment of subjects in the normal group was demographically matched to the subjects in the hepatic impairment groups with respect to age (± 10 years), body weight (± 20%), and gender. Upon completion of Stage 1 (at least 6 evaluable subjects in mild and moderate group, and matching control subjects in the normal group), an interim analysis was conducted pharmacokinetics results from subjects with mild, and moderate hepatic impairment (enrolled in mild and moderate group, respectively) were compared to those from control subjects with normal hepatic function (normal group). Depending on the results of the interim analysis, the study was to be either concluded with no further enrollment or Stage 2 commenced with enrollment of subjects with severe hepatic impairment along with any additional matching controls (normal group) as needed, implementing the same matching criteria as above.

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Centers

Four centers in USA

Objectives:

Primary objective

To compare the PK of a single oral dose of INC280 (capmatinib) in non-cancer subjects with impaired hepatic function to those in non-cancer subjects with normal hepatic function.

Secondary objective

- To assess the plasma protein binding of capmatinib in non-cancer subjects with normal and impaired hepatic functions
- To assess the safety of a single oral dose of capmatinib in non-cancer subjects with normal and impaired hepatic functions.

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

A single oral dose of 200 mg capmatinib (2 × 100 mg tablets) on Day 1

Statistical Methods

Analysis sets

The Full Analysis Set (FAS) and Safety set comprised all subjects who received at least one dose of capmatinib. Subjects were analyzed according to study group determined by the Child-Pugh classification at the screening visit.
The Pharmacokinetic analysis set (PAS) included all subjects who received the study treatment and provide evaluable PK profile.

Pharmacokinetics

Upon completion of mild and moderate impairment groups, as well as matching control group (Stage 1), an interim analysis (IA) was conducted to compare the PK exposure of the two impairment groups to that of the control (Normal) group. A formal statistical analysis was performed using a linear model with study group as a fixed effect, fitted to the log-transformed PK parameters (AUClast, AUCinf and Cmax) to assess the effect of hepatic impairment. Since the interim analysis results did not show a substantial increase in exposure for either mild or moderate impairment group [GMR for AUC (AUCinf and AUClast) and Cmax (test: reference) <3], then subjects with severe impairment were enrolled in Stage 2 of the study along with any additional matching normal controls as needed. At the completion of Stage 2, the above linear model was repeated to compare all hepatic impairment

groups (including Severe) to the Normal group using all data from stages 1 and 2. In the event the study was closed with <6 subjects in the severe impairment group, the linear model was not to include data from the severe group and the comparison between the severe and normal group. The statistical model described above was rerun on the unbound PK parameters (Cmax,u, AUClast,u, and AUCinf,u) for capmatinib.

Safety

Collection of safety data included the frequency and severity of AEs/SAEs, laboratory data, vital signs, and electrocardiograms. The safety summary tables included on-treatment events/assessments collected up to 30 days since the date of last study treatment administration. All safety events/assessments data were listed and those collected after 30 days from treatment discontinuation date were flagged.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:

- Adult male or female subjects with normal or impaired hepatic functions were enrolled in this study.
- Healthy conditions are determined by absence of clinically significant findings in medical history, physical examination, vital signs, and ECGs.
- Hepatic impairment defined by a Child-Pugh score clinically determined and calculated as per the Child-Pugh classification or history of hepatitis C, or histologically by prior liver biopsy showing cirrhosis, or clinically by physical examination (e.g. liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, ascites, presence of asterixis or gynecomastia), or laboratory data, or liver imaging (computed tomography and/or ultrasound and/or magnetic resonance imaging scans) or endoscopic findings

Key exclusion criteria:

- Subjects with contraindication to receiving capmatinib or any drug or metabolites from a similar class as capmatinib
- Subjects with donation or loss of 400 mL or more of blood within 8 weeks prior to dosing
- Subjects with a history or presence of clinically significant electrocardiogram (ECG) abnormalities or clinically significant cardiovascular disease
- Subjects with a positive hepatitis B surface antigen (HBsAg) or hepatitis C test result.
- Subjects with hepatic impairment with an active grade 3 or 4 hepatic encephalopathy within 4 weeks of study entry or clinical evidence of severe ascites (grade ≥ 3 as per Common Terminology Criteria for Adverse Events v4.03)

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Participant Flow Table (full analysis set)

Disposition Reason	Normal N=10 n (%)	Mild N=7 n (%)	Moderate N=8 n (%)	Severe N=6 n (%)	All subjects N=31 n (%)
Completed treatment	10 (100)	7 (100)	8 (100)	6 (100)	31 (100)
Completed study	10 (100)	7 (100)	8 (100)	6 (100)	31 (100)

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Baseline Characteristics (full analysis set)

Demographic Variable	Normal N=10	Mild N=7	Moderate N=8	Severe N=6	All subjects N=31
Age (years)					
Mean (SD)	53.0 (5.58)	56.9 (4.02)	55.0 (7.21)	50.3 (5.85)	53.9 (5.97)
Median	54.5	57.0	56.5	49.0	55.0
Min - Max	43.0 - 62.0	52.0 - 62.0	45.0 - 64.0	44.0 - 60.0	43.0 - 64.0
Age category (years) -n (%)					
<65	10 (100)	7 (100)	8 (100)	6 (100)	31 (100)
Sex -n (%)					
Female	2 (20.0)	0	2 (25.0)	1 (16.7)	5 (16.1)
Male	8 (80.0)	7 (100)	6 (75.0)	5 (83.3)	26 (83.9)
Race -n (%)					
Caucasian	6 (60.0)	4 (57.1)	7 (87.5)	6 (100)	23 (74.2)
Black	4 (40.0)	2 (28.6)	1 (12.5)	0	7 (22.6)
Other	0	1 (14.3)	0	0	1 (3.2)
Ethnicity -n (%)					
Hispanic/Latino	4 (40.0)	1 (14.3)	6 (75.0)	5 (83.3)	16 (51.6)
Other	6 (60.0)	6 (85.7)	2 (25.0)	1 (16.7)	15 (48.4)
Weight (kg)					
Mean (SD)	79.9 (12.93)	81.5 (11.98)	82.8 (14.96)	88.6 (17.88)	82.7 (13.94)
Median	83.6	82.4	82.2	88.7	83.7
Min - Max	56.3 - 100.5	69.4 - 103.9	61.1 - 100.5	60.4 - 114.9	56.3 - 114.9
Height (cm)					
Mean (SD)	171.7 (9.40)	179.4 (6.61)	166.9 (5.87)	171.5 (11.03)	172.2 (9.13)

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Demographic Variable	Normal N=10	Mild N=7	Moderate N=8	Severe N=6	All subjects N=31
Median	173.8	180.0	166.6	176.5	174.0
Min - Max	150.5 - 185.0	170.0 - 187.0	158.0 - 174.1	155.0 - 181.0	150.5 - 187.0
Body surface area (m^2)					
Mean (SD)	2.0 (0.21)	2.0 (0.16)	2.0 (0.20)	2.1 (0.26)	2.0 (0.20)
Median	2.0	2.1	2.0	2.1	2.0
Min - Max	1.6 - 2.3	1.8 - 2.3	1.7 - 2.2	1.7 - 2.4	1.6 - 2.4
Body mass index (kg/m^2)					
Mean (SD)	27.0 (2.54)	25.3 (3.53)	29.7 (5.17)	30.1 (5.04)	27.9 (4.31)
Median	27.9	24.2	28.3	30.2	27.4
Min - Max	21.5 - 29.4	20.8 - 32.1	22.2 - 36.8	23.6 - 35.6	20.8 - 36.8

The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before treatment.
BMI (kg/m^2) = weight (kg) / height $(m)^2$.
BSA (Gehan and George): BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.
BMI and BSA are calculated using the baseline weight and baseline height..

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Summary of Pharmacokinetics (PK)

Primary Outcome Results

Summary of statistical analysis of PK parameters (AUCinf, AUClast, Cmax, Tmax) for capmatinib (Pharmacokinetic analysis set)

PK parameter (unit)	Study group	n*	Adjusted geo-mean	Comparisons	Group comparison		
					Geo-mean ratio	90% CI	
						Lower	Upper
AUCinf (ng*hr/mL)	Normal	9	6240				
	Mild	6	4790	Mild/Normal	0.767	0.532	1.11
	Moderate	8	5700	Moderate/Normal	0.914	0.652	1.28
	Severe	6	7720	Severe/Normal	1.24	0.858	1.78
AUClast (ng*hr/mL)	Normal	9	6190				
	Mild	6	4730	Mild/Normal	0.764	0.529	1.10
	Moderate	8	5660	Moderate/Normal	0.915	0.652	1.28
	Severe	6	7710	Severe/Normal	1.24	0.862	1.80
Cmax (ng/mL)	Normal	9	1740				
	Mild	6	1260	Mild/Normal	0.724	0.476	1.10
	Moderate	8	1440	Moderate/Normal	0.828	0.563	1.22
	Severe	6	1770	Severe/Normal	1.02	0.669	1.55
Tmax (hr)	Normal	9	1.00				
	Mild	6	1.25	Mild-Normal	0.250		
	Moderate	8	1.25	Moderate-Normal	0.250		
	Severe	6	1.50	Severe-Normal	0.500		

Model is a linear model of the log-transformed PK parameters. Included in the model were study group as a fixed effect.
Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.
n* = number of subjects with non-missing values.
For Tmax, median is presented under ‘Adjusted geo-mean’, difference of medians under ‘Geo-mean ratio'.

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Summary of PK parameters for capmatinib by study group (Pharmacokinetic analysis set)

Study group	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
Normal (N=9)	n	9	9	9	9
	Mean (SD)	6930 (3350)	6970 (3340)	1870 (732)	N/A
	CV% mean	48.4	48.0	39.1	N/A
	Geo-mean	6190	6240	1740	N/A
	CV% geo-mean	55.2	54.6	44.1	N/A
	Median	7680	7710	1830	1.00
	[Min; Max]	[2700; 13200]	[2730; 13200]	[822; 3140]	[0.500; 2.00]
Mild (N=6)	n	6	6	6	6
	Mean (SD)	4810 (944)	4870 (992)	1380 (620)	N/A
	CV% mean	19.6	20.4	44.9	N/A
	Geo-mean	4730	4790	1260	N/A
	CV% geo-mean	20.7	21.4	51.5	N/A
	Median	4980	5010	1370	1.25
	[Min; Max]	[3670; 5840]	[3700; 6040]	[658; 2260]	[0.500; 2.00]
Moderate (N=8)	n	8	8	8	8
	Mean (SD)	5920 (1860)	5960 (1890)	1560 (613)	N/A

Study group	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
	CV% mean	31.5	31.7	39.3	N/A
	Geo-mean	5660	5700	1440	N/A
	CV% geo-mean	32.5	32.5	47.3	N/A
	Median	5640	5660	1550	1.25
	[Min; Max]	[3710; 9120]	[3730; 9280]	[660; 2270]	[0.500; 3.00]
Severe (N=6)	N	6	6	6	6
	Mean (SD)	8510 (4410)	8530 (4410)	2020 (1270)	N/A
	CV% mean	51.8	51.8	62.8	N/A
	Geo-mean	7710	7720	1770	N/A
	CV% geo-mean	50.1	50.1	56.6	N/A
	Median	7270	7290	1580	1.50
	[Min; Max]	[4680; 16400]	[4700; 16500]	[950; 4470]	[1.00; 3.00]

n: number of subjects with non-missing values.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log

Secondary Outcome Results

Plasma protein binding of capmatinib

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Summary of fraction unbound of capmatinib in plasma by study group (Pharmacokinetic analysis set)

Scheduled sampling timepoint (hr)	Statistics	Normal (N=9)	Mild (N=6)	Moderate (N=8)	Severe (N=6)	All subjects (N=29)
3 hr post dose	n	9	6	8	6	29
	m	9	6	8	6	29
	Mean (SD)	0.0297 (0.00542)	0.0318 (0.00913)	0.0322 (0.00567)	0.0425 (0.00767)	0.0335 (0.00805)
	CV% mean	18.2	28.7	17.6	18.1	24.1
	Geo-mean	0.0290	0.0310	0.0320	0.0420	0.0330
	CV% geo-mean	19.4	27.8	16.1	17.3	23.5
	Median	0.0299	0.0288	0.0299	0.0414	0.0324
	[Min; Max]	[0.0210; 0.0362]	[0.0237; 0.0467]	[0.0276; 0.0445]	[0.0351; 0.0560]	[0.0210; 0.0560]

n: number of subjects with non-missing values, m: number of non-zero concentrations.

Below the limit of quantitation (BLQ) values (< 1.0 ng/mL) have been set to zero.

Zero concentrations are considered as missing in geometric mean calculations.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

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Summary of statistical analysis of PK parameters (AUCinf, AUClast, Cmax) for capmatinib expressed as unbound drug (Pharmacokinetic analysis set)

					Group comparison		
						90% CI	
PK parameter (unit)	**Hepatic group**	**n***	**Adjusted geo-mean**	**Comparisons**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf,u	Normal	9	183				
	Mild	6	147	Mild/Normal	0.807	0.551	1.18
	Moderate	8	182	Moderate/Normal	0.995	0.700	1.41
	Severe	6	324	Severe/Normal	1.78	1.21	2.60
AUClast,u	Normal	9	181				
	Mild	6	146	Mild/Normal	0.804	0.548	1.18
	Moderate	8	180	Moderate/Normal	0.996	0.700	1.42
	Severe	6	323	Severe/Normal	1.78	1.22	2.62
Cmax,u (ng/mL)	Normal	9	50.9				
	Mild	6	38.8	Mild/Normal	0.761	0.477	1.21
	Moderate	8	45.9	Moderate/Normal	0.901	0.586	1.39
	Severe	6	74.3	Severe/Normal	1.46	0.915	2.33

Model is a linear model of the log-transformed PK parameters. Included in the model were study group as a fixed effect.

Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

n* = number of subjects with non-missing values.

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Summary of Safety

Safety Results

Adverse events, regardless of study drug relationship by primary system organ class, preferred term, maximum grade and study group (Safety Set)

Primary system organ class Preferred term	Normal N=10 n (%)	Mild N=7 n (%)	Moderate N=8 n (%)	Severe N=6 n (%)	All subjects N=31 n (%)
Any primary system organ class	0	3 (42.9)	2 (25.0)	2 (33.3)	7 (22.6)
Grade 1	0	2 (28.6)	2 (25.0)	2 (33.3)	6 (19.4)
Grade 2	0	1 (14.3)	0	0	1 (3.2)
Ear and labyrinth disorders	0	1 (14.3)	0	0	1 (3.2)
Vertigo	0	1 (14.3)	0	0	1 (3.2)
Gastrointestinal disorders	0	0	2 (25.0)	1 (16.7)	3 (9.7)
Nausea	0	0	2 (25.0)	0	2 (6.5)
Diarrhoea	0	0	0	1 (16.7)	1 (3.2)
Flatulence	0	0	0	1 (16.7)	1 (3.2)
General disorders and administration site conditions	0	1 (14.3)	0	0	1 (3.2)
Medical device site dermatitis	0	1 (14.3)	0	0	1 (3.2)
Infections and infestations	0	0	0	1 (16.7)	1 (3.2)
Urinary tract infection	0	0	0	1 (16.7)	1 (3.2)
Metabolism and nutrition disorders	0	1 (14.3)	0	0	1 (3.2)
Hypoglycaemia	0	1 (14.3)	0	0	1 (3.2)
Nervous system disorders	0	1 (14.3)	1 (12.5)	0	2 (6.5)
Headache	0	1 (14.3)	1 (12.5)	0	2 (6.5)

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Primary system organ class Preferred term	Normal N=10 n (%)	Mild N=7 n (%)	Moderate N=8 n (%)	Severe N=6 n (%)	All subjects N=31 n (%)
Dizziness	0	0	1 (12.5)	0	1 (3.2)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All Subjects'.
A subject with multiple occurrences of an AE under one study group is counted only once in the AE category for that study group.
A subject with multiple severity ratings for an AE while on a study group, is only counted under the maximum rating.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row at maximum severity grade.

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Other Relevant Findings

None

Conclusion:

No significant safety findings were reported in this study; no deaths, SAEs, or other significant AEs occurred during the study.

Subjects with mild hepatic impairment have a slightly lower exposure to capmatinib than subjects with normal hepatic function. Subjects with moderate hepatic impairment have similar exposure and subjects with severe hepatic impairment have 24% higher exposure compared with normal hepatic function. In summary, compared to the normal group, the mild, moderate and severe hepatic impaired groups did not show significant change in exposure to capmatinib.

Date of Clinical Trial Report

25-Apr-2018