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Sponsor

Novartis

Generic Drug Name

Asciminib

Trial Indication(s)

Impaired Hepatic Function

Protocol Number

CABL001A2103

Protocol Title

A Phase I, open-label, multi-center, single-dose study to evaluate the pharmacokinetics of ABL001 in healthy subjects with normal hepatic function and subjects with impaired hepatic function

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

03-May-2016 (first subject first visit)
20-Jul-2017 (last subject last visit)

Study Design/Methodology

This was a Phase I, multi-center, open-label, single oral dose study to assess the pharmacokinetics (PK) of ABL001 in subjects with impaired hepatic function and in healthy subjects with normal hepatic function. A total of 32 subjects (eight evaluable subjects for PK per group) were assigned according to their hepatic function on the basis of Child-Pugh classification: normal (Group 1: Control), mild (Group 2: Child-Pugh A), moderate (Group 3: Child-Pugh B) and severe (Group 4: Child-Pugh C) hepatic impairment. A single dose of 40 mg asciminib was provided at Day 1. The total study duration for each subject was approximately 7-weeks, which consisted of a 3-week screening/baseline period (Day -21 to Day -1), a treatment period (Day 1 to Day 3), an end-of treatment-visit and a 30-day post-ABL001 dose safety follow-up period.

Centers.

Three centers in one country: USA

Objectives:

Primary Objective: To evaluate the PK of a single oral dose of asciminib in subjects with various degrees of impaired hepatic function (by Child-Pugh classification) relative to healthy subjects.

Secondary Objective:

- To evaluate the safety and tolerability of a single oral dose of asciminib in healthy subjects with normal hepatic function and subjects with various degrees of impaired hepatic function.
- To evaluate asciminib plasma protein binding in healthy subjects with normal hepatic function and subjects with various degrees of impaired hepatic function.
- To evaluate asciminib PK expressed as unbound drug in subjects with various degree of impaired hepatic function relative to healthy subjects.

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

Day 1: asciminib 40mg per oral

Statistical Methods

A formal comparison was conducted for the primary PK parameters (AUCinf, AUClast and Cmax). Using data from the mild, moderate, severe, and normal groups, a linear model was fitted to the log-transformed PK parameters to evaluate the pharmacokinetics of a single oral dose of asciminib in subjects with various degrees of impaired hepatic function (by Child-Pugh classification) relative to healthy subjects. The model included treatment as a fixed factor. A point estimate and the corresponding two-sided 90% confidence interval (CI) for the treatment differences (mild, moderate and severe as test vs. normal as reference) was calculated. The point estimate and CI were anti-log transformed to obtain the point estimate and the 90% confidence interval for the geometric mean ratio on the original scale.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Hepatically impaired subjects and matching healthy subjects are the preferred study population for this study.
- Male subjects and sterile or post-menopausal female healthy subjects between 18 and 75 years of age and patients with Child-Pugh Clinical Assessment Score as calculated per the Child-Pugh classification.
- Healthy subjects with adequate end organ function and laboratory values within the reference range at the local laboratory, unless deemed not clinically significant by the Investigator and approved by the Sponsor were the main inclusion criteria.

Exclusion criteria

- Presence of clinically significant ECG abnormalities or a family history or presence of prolonged QT-interval syndrome, History of cardiac disease, History of malignancy of any organ system, Administration of strong or moderate CYP3A4 inhibitors or inducers within 14 days prior to dosing were some of the main exclusion criteria.

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Participant Flow Table

Subject disposition (Full Analysis Set)

	Normal N=8 n (%)	Mild N=8 n (%)	Moderate N=8 n (%)	Severe N=8 n (%)	All subjects N=32 n (%)
Subjects treated					
Treated	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100)
Completed treatment	8 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	32 (100)

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Baseline Characteristics

Demographics and other baseline characteristics (Full Analysis Set)

Demographic Variable		Normal N=8	Mild N=8	Moderate N=8	Severe N=8	All subjects N=32
Age (years)						
	n	8	8	8	8	32
	Mean (SD)	54.9 (4.52)	57.6 (6.80)	57.9 (6.06)	58.6 (6.55)	57.3 (5.92)
	Median	55.0	56.0	58.5	60.0	56.5
	Q1-Q3	52.5-58.0	53.0-63.5	53.5-63.0	56.0-63.5	53.5-62.0
	Min - Max	47-61	48-68	48-65	45-65	45-68
Age category –n (%)						
	18 to <65 years	8 (100)	6 (75.0)	7 (87.5)	6 (75.0)	27 (84.4)
	65 to <85 years	0	2 (25.0)	1 (12.5)	2 (25.0)	5 (15.6)
Sex –n (%)	Male	6 (75.0)	7 (87.5)	7 (87.5)	6 (75.0)	26 (81.3)
	Female	2 (25.0)	1 (12.5)	1 (12.5)	2 (25.0)	6 (18.8)
Race –n (%)	Caucasian	6 (75.0)	6 (75.0)	7 (87.5)	8 (100)	27 (84.4)
	Black	2 (25.0)	2 (25.0)	1 (12.5)	0	5 (15.6)
Ethnicity –n (%)	Hispanic or Latino	3 (37.5)	5 (62.5)	5 (62.5)	4 (50.0)	17 (53.1)
	Other	5 (62.5)	3 (37.5)	3 (37.5)	4 (50.0)	15 (46.9)
Weight (kg)						
	n	8	8	8	8	32
	Mean (SD)	87.58 (14.497)	88.01 (12.355)	86.16 (13.093)	75.94 (12.886)	84.42 (13.542)
	Median	89.35	86.20	89.65	75.90	83.75
	Q1-Q3	73.75-100.60	79.30-94.60	78.40-94.40	65.50-84.05	73.65-95.55
	Min - Max	68.5-104.7	73.0-110.9	61.8-102.6	59.3-97.3	59.3-110.9
Height (cm)						

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Demographic Variable		Normal N=8	Mild N=8	Moderate N=8	Severe N=8	All subjects N=32
	n	8	8	8	8	32
	Mean (SD)	174.9 (7.34)	171.4 (7.50)	171.4 (6.32)	163.6 (6.74)	170.3 (7.85)
	Median	176.0	169.5	172.0	163.5	170.0
	Q1-Q3	171.5-178.5	166.4-179.5	167.8-176.5	159.5-169.0	165.0-178.0
	Min - Max	161-186	160-180	160-179	152-173	152-186
Body mass index (kg/m2)						
	n	8	8	8	8	32
	Mean (SD)	28.63 (4.423)	30.03 (4.181)	29.30 (4.179)	28.40 (4.706)	29.09 (4.210)
	Median	28.82	28.47	29.15	29.06	28.84
	Q1-Q3	24.91-31.57	26.48-34.54	27.10-32.36	23.72-31.67	25.97-32.56
	Min - Max	22.7-35.8	25.6-35.6	22.0-35.2	22.7-35.5	22.0-35.8

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Summary of Efficacy

Primary Outcome Result(s)

Statistical analysis of primary PK parameters for asciminib (Pharmacokinetic Analysis Set)

					Treatment comparison 90% CI		
PK parameter (unit)	**Treatment**	**n***	**Adjusted geo-mean**	**Comparison(s)**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (ng*hr/mL)	Normal	8	4910				
	Mild	8	5980	Mild/Normal	1.22	0.964	1.54
	Moderate	8	5050	Moderate/Normal	1.03	0.813	1.30
	Severe	7	8160	Severe/Normal	1.66	1.30	2.12
AUClast (ng*hr/mL)	Normal	8	4840				
	Mild	8	5860	Mild/Normal	1.21	0.960	1.53
	Moderate	8	4960	Moderate/Normal	1.03	0.812	1.30
	Severe	8	7470	Severe/Normal	1.55	1.22	1.95
Cmax (ng/mL)	Normal	8	578				
	Mild	8	731	Mild/Normal	1.26	1.05	1.52
	Moderate	8	568	Moderate/Normal	0.983	0.819	1.18
	Severe	8	746	Severe/Normal	1.29	1.08	1.55

Model is a linear model of the log-transformed PK parameters. Included in the model was treatment as a fixed effect.

Results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.

n* = number of observations used for analysis.

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Primary PK parameters for asciminib (Pharmacokinetic Analysis Set)

Parameter	Statistics	Normal N=8	Mild N=8	Moderate N=8	Severe N=8
AUCinf (ng*hr/mL)	n	8	8	8	7
	Mean (SD)	5000 (1020)	6320 (2560)	5170 (1210)	8490 (2490)
	CV%	20.4	40.5	23.3	29.3
	Geo-mean	4910	5980	5050	8160
	Geo-CV%	21.1	34.2	23.8	32.0
	Median	4700	5840	5020	8680
	Min-Max	3360-6500	4040-12300	3450-7180	5280-11200
AUClast (ng*hr/mL)	n	8	8	8	8
	Mean (SD)	4930 (1010)	6170 (2400)	5070 (1150)	7810 (2420)
	CV%	20.4	38.8	22.7	31.0
	Geo-mean	4840	5860	4960	7470
	Geo-CV%	21.0	33.3	23.3	32.4
	Median	4620	5760	4920	7560
	Min-Max	3330-6400	3960-11700	3420-6900	5180-11000
Cmax (ng/mL)	n	8	8	8	8
	Mean (SD)	584 (89.0)	743 (143)	573 (77.1)	782 (266)
	CV%	15.2	19.3	13.5	34.0
	Geo-mean	578	731	568	746
	Geo-CV%	15.1	19.0	14.0	33.2
	Median	583	742	584	694
	Min-Max	491-736	578-1010	448-660	479-1260

n = number of subjects with corresponding evaluable PK parameters.

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Secondary PK parameters for asciminib (Pharmacokinetic Analysis Set)

Parameter	Statistics	Normal N=8	Mild N=8	Moderate N=8	Severe N=8
Tmax (hr)	n	8	8	8	8
	Mean (SD)	NA	NA	NA	NA
	CV%	NA	NA	NA	NA
	Geo-mean	NA	NA	NA	NA
	Geo-CV%	NA	NA	NA	NA
	Median	2.00	2.00	2.00	1.50
	Min-Max	1.00-4.00	1.75-3.00	1.00-4.00	1.00-4.00
T1/2 (hr)	n	8	8	8	7
	Mean (SD)	14.2 (1.85)	15.7 (1.96)	13.4 (3.11)	17.8 (3.55)
	CV%	13.0	12.5	23.3	20.0
	Geo-mean	14.1	15.6	13.0	17.5
	Geo-CV%	13.6	12.2	26.3	19.9
	Median	14.6	14.9	13.5	16.6
	Min-Max	11.3-16.4	13.4-19.1	7.67-17.7	13.1-23.5
CL/F (L/hr)	n	8	8	8	7
	Mean (SD)	8.31 (1.79)	6.98 (1.96)	8.12 (1.92)	5.12 (1.64)
	CV%	21.6	28.1	23.7	32.1
	Geo-mean	8.15	6.69	7.93	4.90
	Geo-CV%	21.1	34.2	23.8	32.0
	Median	8.51	6.86	7.98	4.61
	Min-Max	6.16-11.9	3.25-9.90	5.57-11.6	3.57-7.58
Vz/F (L)	n	8	8	8	7
	Mean (SD)	170 (40.3)	159 (55.4)	152 (31.7)	129 (40.2)
	CV%	23.7	34.8	20.9	31.1
	Geo-mean	165	151	149	124
	Geo-CV%	26.1	37.4	21.5	32.1
	Median	177	144	147	122
	Min-Max	104-228	79.8-252	104-196	80.2-190

n = number of subjects with corresponding evaluable PK parameters.

Secondary Outcome Result(s)

Plasma protein unbound fraction (%) (Pharmacokinetic analysis set)

Scheduled sampling timepoint	Statistics	Normal N=8	Mild N=8	Moderate N=8	Severe N=8
2 hr					
	n	8	8	8	8
	m	8	8	8	8
	Mean (SD)	0.00918 (0.000698)	0.00882 (0.00185)	0.00930 (0.000927)	0.00864 (0.00160)
	CV%	7.6	21.0	10.0	18.5
	Geo-mean	0.00916	0.00864	0.00926	0.00851
	Geo-CV%	7.6	22.6	10.1	19.7
	Median	0.00920	0.00914	0.00927	0.00924
	Min-Max	0.00818-0.0104	0.00591-0.0116	0.00798-0.0105	0.00615-0.0106

n = number of subjects with evaluable values, m = number of non-zero concentrations.
Zero concentrations are considered as missing in Geo-mean and Geo-CV% calculations.

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Unbound primary PK parameters for asciminib (Pharmacokinetic analysis set)

Parameter	Statistics	Normal N=8	Mild N=8	Moderate N=8	Severe N=8
(AUCinf)u (ng*hr/mL)	n	8	8	8	7
	Mean (SD)	0.456 (0.0841)	0.538 (0.153)	0.482 (0.134)	0.701 (0.181)
	CV%	18.4	28.5	27.8	25.8
	Geo-mean	0.450	0.517	0.467	0.679
	Geo-CV%	18.6	32.3	26.3	28.2
	Median	0.434	0.571	0.446	0.695
	Min-Max	0.329-0.598	0.273-0.808	0.361-0.746	0.415-0.986
(AUClast)u (ng*hr/mL)	n	8	8	8	8
	Mean (SD)	0.449 (0.0827)	0.526 (0.145)	0.473 (0.127)	0.654 (0.166)
	CV%	18.4	27.6	26.8	25.3
	Geo-mean	0.443	0.506	0.459	0.636
	Geo-CV%	18.5	31.7	25.6	26.6
	Median	0.425	0.564	0.437	0.659
	Min-Max	0.326-0.589	0.269-0.771	0.356-0.717	0.402-0.943
(Cmax)u (ng/mL)	n	8	8	8	8
	Mean (SD)	0.0535 (0.00799)	0.0649 (0.0145)	0.0532 (0.00828)	0.0645 (0.0119)
	CV%	14.9	22.4	15.6	18.5
	Geo-mean	0.0530	0.0632	0.0526	0.0634
	Geo-CV%	14.7	27.3	16.2	19.6
	Median	0.0538	0.0667	0.0535	0.0648
	Min-Max	0.0434-0.0677	0.0345-0.0832	0.0403-0.0630	0.0473-0.0775

n = number of subjects with corresponding evaluable PK parameters.

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Summary of Safety

Safety Results

Adverse events by system organ class and preferred term (Safety set)

Primary system organ class Preferred term	Normal N=8 n (%)	Mild N=8 n (%)	Moderate N=8 n (%)	Severe N=8 n (%)	All subjects N=32 n (%)
Number of subjects with at least one event	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	4 (12.5)
Metabolism and nutrition disorders	0	0	1 (12.5)	0	1 (3.1)
Hypoglycaemia	0	0	1 (12.5)	0	1 (3.1)
Nervous system Disorders	1 (12.5)	1 (12.5)	0	1 (12.5)	3 (9.4)
Headache	1 (12.5)	0	0	1 (12.5)	2 (6.3)
Somnolence	0	1 (12.5)	0	0	1 (3.1)

Numbers (n) represent counts of subjects.

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Non-serious adverse events (threshold = 5%) by system organ class and preferred term (Safety set)

Primary system organ class Preferred term	Normal N=8	Mild N=8	Moderate N=8	Severe N=8	All subjects N=32
Total number of subjects affected	1 / 8 (12.5)	1 / 8 (12.5)	1 / 8 (12.5)	1 / 8 (12.5)	4 / 32 (12.5)
Subjects affected by non-serious adverse events / exposed (%)					
Metabolism and nutrition disorders					
Hypoglycaemia Subjects affected / exposed (%)	0 / 8 (0.0)	0 / 8 (0.0)	1 / 8 (12.5)	0 / 8 (0.0)	1 / 32 (3.1)
Occurrences (all)	0	0	1	0	1
Nervous system disorders					
Headache Subjects affected / exposed (%)	1 / 8 (12.5)	0 / 8 (0.0)	0 / 8 (0.0)	1 / 8 (12.5)	2 / 32 (6.3)
Occurrences (all)	1	0	0	1	2
Somnolence Subjects affected / exposed (%)	0 / 8 (0.0)	1 / 8 (12.5)	0 / 8 (0.0)	0 / 8 (0.0)	1 / 32 (3.1)
Occurrences (all)	0	1	0	0	1

Total number of subjects affected by non-serious AEs are those subjects who had at least one preferred term that met the threshold criteria.
Preferred terms with a frequency greater than 5% in any treatment arm were printed.

Serious Adverse Events and Deaths

No deaths, other significant adverse events (AEs), or AEs leading to study drug discontinuation were reported.

One serious adverse event (SAE) was reported in the study, but considered not related to the study treatment by the Investigator since it occurred prior to starting the study medication. This subject was in the severe hepatic impairment group, had a grade 3 adverse event of Cellulitis prior to the start of study medication; the event recovered prior to start of study medication.

Conclusion:

- Compared to the normal group, mild hepatic impairment group exhibited a trend to slightly higher exposure with 22% higher AUCinf, 21% higher AUClast, 26% higher Cmax, although considered globally comparable to normal subjects; moderate hepatic impairment group had similar exposure; severe hepatic impairment group had 66% higher AUCinf, 55% higher AUClast, 29% higher Cmax. Median asciminib Tmax values for normal, mild, moderate groups were same (2 hours) and severe hepatic impairment group was 1.5 hours.

- Protein binding of asciminib was similar across groups.

- Based on the unbound fraction of asciminib, the mild hepatic impairment group had 15% higher AUCinf, 14% higher AUClast, 19% higher Cmax; moderate hepatic impairment group had similar exposure; severe hepatic impairment group had 51% higher AUCinf, 44% higher AUClast, 20% higher Cmax.

- Treatment with asciminib 40 mg was well tolerated in healthy subjects and also in subjects with varying degrees of hepatic impairment.

Date of Clinical Trial Report

9 May 2018