Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Asciminib

Trial Indication(s)

Renal Impairment

Protocol Number

CABL001A2105

Protocol Title

A phase I, open-label and single-dose study to evaluate the pharmacokinetics and safety of a single 40 mg oral dose of ABL001 (asciminib) in subjects with impaired renal function compared to matched control subjects with normal renal function

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 3 drug development

Study Start/End Dates

Study Start Date: November 2018 (Actual)
Primary Completion Date: March 2019 (Actual)

Study Completion Date: April 2019 (Actual)

Reason for Termination (If applicable)

NA

Study Design/Methodology

This was a Phase I, open label, 2-stage, single dose study to evaluate the PK and safety of a single oral dose of asciminib in subjects with impaired renal function compared to matched control subjects with normal renal function.

The study was divided in two stages and conducted in a staggered manner. In Stage 1, the effects of impaired renal function on the PK of asciminib were evaluated by comparing the PK in subjects with severe renal impairment (aGFR<30 mL/min) not yet requiring dialysis to subjects with normal renal function (aGFR>=90 mL/min). An interim analysis was planned to take place after completion of Stage 1. If the point estimate of the geometric mean ratios of either asciminib AUC (AUCinf or AUClast) or asciminib Cmax between subjects in the severe renal impairment cohort and subjects in the normal renal function cohort is ≥2, the study will be expanded into Stage 2. As the ratios observed in the Stage 1 of the study (in the interim analysis) were below the threshold of 2 there was no need to initiate the Stage 2 and the study was considered completed.

Centers

2 centers in 2 countries: Bulgaria(1), Germany(1)

Objectives:

Objectives:

Primary objective: To evaluate the effect of impaired renal function on the PK of a single oral dose of asciminib relative to subjects with normal renal function.

Secondary objectives:

 To evaluate the safety and tolerability of a single oral dose of asciminib in subjects with impaired renal function and subjects with normal renal function.

 To evaluate asciminib PK expressed as unbound drug in subjects with impaired renal function and subjects with normal renal function.
 To evaluate the effect of impaired renal function on secondary PK parameters of asciminib.
 To evaluate asciminib plasma protein binding in subjects with impaired renal function and subjects with normal renal function.

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

The investigational drug, asciminib, was supplies as 40 mg oral tablets. Each subject received a single dose of asciminib (40 mg tablet) on Day 1 with 240 mL of non-carbonated water

Statistical Methods

Asciminib exposure in the severe renal impairment cohort was compared to the exposure in the normal renal function cohort. A formal comparison was conducted using the primary PK parameters (Cmax, AUClast, AUCinf, and CL/F). Each of these PK parameters were modeled on the log scale by means of an analysis of variance (ANOVA) model including study cohort as a fixed effect. Point estimates and the corresponding 90% confidence intervals (CIs) for the mean difference between the matching control cohort and the severe renal impairment cohort were calculated. This was anti-logged to obtain the point estimate and 90% CI for the ratio of the geometric means on the original scale. Concentrations and PK parameters for asciminib were summarized by study cohort. Each of these PK parameters [(Cmax)u, (CL/F)u, (AUClast)u, and (AUCinf)u] were modeled on the log scale by means of an ANOVA model including study cohort as a fixed effect. Point estimates and the corresponding 90% CIs for the mean difference between the matching control cohort and the severe renal impairment cohort were calculated. This was anti-logged to obtain the point estimate and 90% CI for the ratio of the geometric means on the original scale.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Male or sterile / post-menopausal female
- BMI between 18 and 36 kg/m2, body weight greater than or equal to 50 kg and no more than 120 kg
- Adequate venous access for blood sampling
- For healthy volunteers: subject must be matched to at least one renal impaired subject by age (+/- 10 years), body weight (+/- 20%) and gender

- For renal impaired subjects: documented stable renal disease without evidence of progressive decline in renal function (stable renal disease is defined as no significant change, such as, stable aGFR < 90, for 12 weeks prior to study entry)

Exclusion Criteria:
- women of child-bearing potential / pregnant / nursing
- contraindication or hypersensitivity to any drug or metabolites from similar class as asciminib or to any excipients of the study drug
- cardiac or cardiac repolarization abnormality
- history of psychiatric illness within the past 2 years
- history of acute or chronic pancreatitis
- subject on dialysis
- smokers (use of tobacco products in the previous 3 months) and not willing to abstain from using tobacco during the study
- any surgical or medical condition altering the absorption, distribution, metabolism or excretion of drug
- history of immunodeficiency diseases, including a positive Human Immunodeficiency Virus (HIV) test result at screening
- chronic infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) at screening
- donation or loss of 400 mL or more of blood or plasma within 8 weeks prior to dosing or other amount considered to compromise the health of the subject if previous history of anemia exists
- use of the following drugs within 28 days prior to dosing: drugs that prolong the QT interval; CYP3A4 inhibitors and inducers; BCRP, UGT and PgP inhibitors and inducers

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Overall Study

	Normal renal function	Severe renal impairment	Total
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment	
Started	6	8	14
Completed	6	8	14

Not Completed	0	0	0

Baseline Characteristics

	Normal renal function	Severe renal impairment	Total
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment	
Number of Participants [units: participants]	6	8	14
Age Continuous (units: years) Mean ± Standard Deviation			
	59.0±8.39	56.9±6.77	57.8±7.28
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	2	3	5
Male	4	5	9
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
White	6	8	14

Summary of Efficacy

NA

Primary Outcome Result(s)

Pharmacokinetics: AUCinf derived from Plasma concentration of asciminib

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Pharmacokinetics: AUCinf derived from Plasma concentration of asciminib (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	5550 (28.7%)	8630 (50.7%)

Statistical Analysis

Groups	Normal renal function, Severe renal impairment	AUC inf
Non-Inferiority/Equivalence Test	Equivalence	linear model of the log transformed PK parameters
Method	ANOVA	
Other ratio geometric mean	1.56	

90 % Confidence Interval 2-Sided	1.05 to 2.30

Pharmacokinetics: AUClast derived from Plasma concentration of asciminib

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Pharmacokinetics: AUClast derived from Plasma concentration of asciminib (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	5480 (28.5%)	8180 (50.0%)

Statistical Analysis

Groups	Normal renal function, Severe renal impairment	AUC last
Non-Inferiority/Equivalence Test	Other	linear model of the log transformed PK parameters
Method	ANOVA	
Other ratio geometric mean	1.49	

90 % Confidence Interval 2-Sided	1.01 to 2.20

Pharmacokinetics: CMax derived from Plasma concentration of asciminib

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Pharmacokinetics: CMax derived from Plasma concentration of asciminib (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	564 (30.0%)	607 (52.1%)

Statistical Analysis

Groups	Normal renal function, Severe renal impairment	Cmax
Non-Inferiority/Equivalence Test	Other	linear model of log transformed PK parameters
Method	ANOVA	
Other ratio geometric mean	1.08	

90 % Confidence Interval 2-Sided	0.719 to 1.61

Pharmacokinetics: Clearance of asciminib from plasma by CL/F

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Pharmacokinetics: Clearance of asciminib from plasma by CL/F (units: L/h) Geometric Mean (Geometric Coefficient of Variation)		
	7.21 (28.7%)	4.64 (50.7%)

Statistical Analysis

Groups	Normal renal function, Severe renal impairment	CL/F
Non-Inferiority/Equivalence Test	Other	linear model of the log transformed PK parameters
Method	ANOVA	
Other ratio geometric mean	0.643	

90 % Confidence Interval 2-Sided	0.434 to 0.952

Secondary Outcome Result(s)

Asciminib PK parameters unbound AUClast (AUClast)u and unbound AUCinf (AUCinf)u based on unbound fraction in plasma.

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Asciminib PK parameters unbound AUClast (AUClast)u and unbound AUCinf (AUCinf)u based on unbound fraction in plasma. (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
AUCinf unbound	68.6 (26.4%)	109 (44.1%)
AUClast unbound	67.7 (26.3%)	103 (43.5%)

Asciminib PK parameters unbound Cmax (Cmax)u based on unbound fraction in plasma

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment

Number of Participants Analyzed [units: participants]	6	8
Asciminib PK parameters unbound Cmax (Cmax)u based on unbound fraction in plasma (units: ng/mL) Geometric Mean (Geometric Coefficient of Variation)		
	6.97 (27.7%)	7.64 (51.1%)

Asciminib secondary PK parameters T1/2

(Time Frame: 72 hours post-dose)

	Normal renal function	**Severe renal impairment**
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Asciminib secondary PK parameters T1/2 (units: hour) Geometric Mean (Geometric Coefficient of Variation)		
T1/2	12.5 (21.9%)	17.1 (35.4%)

Asciminib secondary PK parameters Tmax

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Asciminib secondary PK parameters Tmax (units: hour) Median (Full Range)		
	2.03 (1.02 to 2.05)	2.00 (2.00 to 8.00)

Unbound Asciminib secondary PK parameter AUC0-72h

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Unbound Asciminib secondary PK parameter AUC0-72h (units: ng*hr/mL) Geometric Mean (Geometric Coefficient of Variation)		
	67.7 (26.3%)	103 (43.5%)

Asciminib secondary PK parameters Vz/F

(Time Frame: 72 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Asciminib secondary PK parameters Vz/F (units: L) Geometric Mean (Geometric Coefficient of Variation)		
asciminib	130 (36.6%)	114 (63.5%)
Unbound asciminib	10500 (37.0%)	9070 (56.4%)

Plasma protein binding as expressed by unbound fraction for asciminib in plasma

(Time Frame: 2 hours post-dose)

	Normal renal function	Severe renal impairment
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Number of Participants Analyzed [units: participants]	6	8
Plasma protein binding as expressed by unbound fraction for asciminib in plasma (units: fraction unbound)		

Geometric Mean (Geometric Coefficient of Variation)		
	1.24 (16.1%)	1.26 (19.0%)

Summary of Safety

Single oral dose of 40 mg asciminib was safe and well tolerated in subjects with severe renal impairment and matching normal renal function subjects.

- Seven subjects (50.0%) (1 subject in normal renal function cohort and 6 subjects in severe renal impairment cohort) had at least one AE in the study.
- Amylase increased and neutropenia were reported in 3 subjects (37.5%) each in the severe renal impairment cohort. In one of the subjects, neutropenia was grade 3.
- Five subjects (35.7%) (1 subject in the normal renal function cohort and 4 subjects in the severe renal impairment cohort) had treatment related AEs in the study.
- One subject in the severe renal impairment cohort had a grade 3 neutrophils count decreased (related to study treatment) on Day 2, which was resolved on Day 36 without any action taken.
- No deaths, SAEs, and other significant AEs were reported during the study.
- No clinically meaningful changes in clinical chemistry, vital signs or ECG were noted

Safety Results

All-Cause Mortality

	Normal renal function N = 6	Severe renal impairment N = 8
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment

Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (22.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Normal renal function N = 6	**Severe renal impairment N = 8**
Arm/Group Description	healthy volunteers with normal renal function	subjects with severe renal impairment
Total participants affected	1 (16.67%)	6 (75.00%)
Blood and lymphatic system disorders		
Neutropenia	0 (0.00%)	3 (37.50%)
Gastrointestinal disorders		
Nausea	1 (16.67%)	0 (0.00%)

Investigations		
Amylase increased	0 (0.00%)	3 (37.50%)
Lipase increased	0 (0.00%)	1 (12.50%)
Nervous system disorders		
Dizziness	1 (16.67%)	0 (0.00%)
Headache	0 (0.00%)	2 (25.00%)

Other Relevant Findings

NA

Conclusion:

Compared to the normal renal function cohort, severe renal impairment cohort had 56% higher AUCinf, 49% higher AUClast and comparable Cmax. Asciminib was well tolerated in this study.

Date of Clinical Trial Report

28-Nov-2019